ACCESSION NUMBER: 1998:27406 CAPLUS
DOCUMENT NUMBER: 128:100929
TITLE: Suppression of murine type II collagen-induced arthritis by interleukin 12
AUTHOR(S): Yamazaki, Jyunko; Kasama, Tsuyoshi; Miwa, Yusuke; Hanyuuda, Michio; Hatano, Yoshimi; Kobayashi, Kazuo; Negishi, Masao; Ide, Hirotsugu; Adachi, Mitsuru
CORPORATE SOURCE: First Dept. of Internal Medicine, Showa Univ. School of Medicine, Tokyo, 142, Japan
SOURCE: Ensho (1997), 17(6), 549-555
CODEN: ENSHEE; ISSN: 0389-4290
PUBLISHER: Nippon Ensho Gakkai Jimukyoku
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB In the present study, we examd. the effect of interleukin 12 (IL-12) on the evolution of murine type II collagen-induced arthritis (CIA). CIA mice injected i.p. with IL-12 (500 ng/mouse/d) demonstrated delayed onset and reduced severity of arthritis. Although IL-12 administration augmented lymphocyte proliferation and interferon-.gamma. prodn. against specific and non-specific stimulation, anti-collagen antibody prodn. was significantly suppressed in CIA, as compared with control mice. Since **IL-12** induced the **prodn**. of serum **tumor necrosis factor** (**TNF**)-.alpha. and corticosterone, the suppression of CIA by IL-12 may, in part, depend upon the augmentation of serum corticosterone, induced by endogenous **TNF**-.alpha.. These data suggest that IL-12 is an important immunomodulator of the pathogenesis of CIA, which acts by regulating not only the humoral and cellular immune responses, but also the expression of immunoregulatory mediators.

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=> s tumor necrosis factor or TNF
L1      187760 TUMOR NECROSIS FACTOR OR TNF

=> s interleukin-12 or IL-12
L2       22391 INTERLEUKIN-12 OR IL-12

=> s l1 and l2
L3        6678 L1 AND L2

=> s l1 (s) l2
L4        4764 L1 (S) L2

=> s produc?
   4 FILES SEARCHED...
L5     9931087 PRODUC?

=>  s l4 (s) l5
L6        2579 L4 (S) L5

=> s l6 and py>1999
L7        1128 L6 AND PY>1999

=> s l6 and py>1998
L8        1582 L6 AND PY>1998

=> s l6 not py>1999
L9        1451 L6 NOT PY>1999

=> s l6 not py>1998
L10        997 L6 NOT PY>1998

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11         509 DUP REM L10 (488 DUPLICATES REMOVED)

=> d ibib abs kwic 1-5

L11  ANSWER 1 OF 509  USPATFULL
ACCESSION NUMBER:       1998:162547  USPATFULL
TITLE:                  Protein kinase inhibitor
INVENTOR(S):            Sriram, Subramaniam, Nashville, TN, United States
                        Bright, John, Nashville, TN, United States
                        Nag, Bishwajit, Fremont, CA, United States
```

	Sharma, Somesh D., Los Altos, CA, United States
PATENT ASSIGNEE(S):	Natpro, Inc., Union City, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5854285		19981229
APPLICATION INFO.:	US 1997-825662		19970403 (8)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	MacMillan, Keith D.
LEGAL REPRESENTATIVE:	Fish & Richardson P.C.
NUMBER OF CLAIMS:	7
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	6 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT:	265

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A compound of the formula I ##STR1## wherein A and C are independently H, alkyl of 1-6 carbon atoms, hydroxy, or alkoxy of 1-6 carbon atoms;

B is hydroxy or alkoxy of 1-6 carbon atoms; and

Y is cyano, ##STR2##

--C(NR.sub.1 R.sub.2).dbd.C(CN).sub.2 ;

wherein X=O or S, and R.sub.1 and R.sub.2 are independently H, benzyl, --CH(CH.sub.3), C.sub.6 H.sub.5

--(CH.sub.2).sub.n C.sub.6 H.sub.6, phenyl; --CO.sub.2 R;

n=2-4; R is lower alkyl of 1-6 carbon atoms

is used for treating inflammation and immunological diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . of both inflammation and providing the necessary "help" for T cell stimulation and proliferation. Most importantly macrophages make IL 1, **IL 12** and **TNF**.alpha. all of which are potent pro-inflammatory molecules and also provide help for T cells. In addition, activation of macrophages results. . . (COX II), nitric oxide (NO) and other free radicals capable of damaging normal cells. Many factors activate macrophages, including bacterial **products**, superantigens and interferon gamma (IFN.gamma.). It is believed that PTK's and other undefined cellular kinases are involved in the activation. . .

L11 ANSWER 2 OF 509 USPATFULL

ACCESSION NUMBER:	1998:161973 USPATFULL
TITLE:	Methods of treating established colitis using antibodies against IL-12
INVENTOR(S):	Strober, Warren, Bethesda, MD, United States Fuss, Ivan, Bethesda, MD, United States Neurath, Markus, Mainz, Germany, Federal Republic of
PATENT ASSIGNEE(S):	The United States of America, as represented by the Department of Health & Human Services, Washington, DC, United States (U.S. government)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5853697		19981229

APPLICATION INFO.: US 1995-547979 19951025 (8)
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Eisenschenk, Frank C.
ASSISTANT EXAMINER: Rabin, Evelyn
LEGAL REPRESENTATIVE: Needle & Rosenberg, P.C.
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 959
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a method for treating the inflammatory response of an established colitis in a subject with inflammatory bowel disease (IBD), comprising administering to a subject diagnosed with an established colitis from an IBD an amount of an antibody to **interleukin-12** effective in reducing the colitis-inducing effect of **interleukin-12**. Also provided is a method for screening a substance for its effectiveness in reducing the inflammatory response of an established colitis comprising obtaining an animal having an established colitis; administering the substance to an animal; and assaying the animal for an effect on **interleukin-12** which results in the reduction of the inflammatory response of the colitis, an amount of reduction of the inflammatory response greater than the amount of reduction **produced** by the administration of antibodies against interferon-gamma or **tumor necrosis factor**-alpha indicating an effective substance. Additionally, the present invention provides a method for screening a substance for its effectiveness in preventing inflammatory bowel disease comprising administering the substance to an animal susceptible to colitis; subjecting the animal to a treatment that will induce a colitis; assaying the animal for the development of a colitis; and comparing the effectiveness of the substance in preventing development of a colitis to the effectiveness of antibodies to interferon-gamma or **tumor necrosis factor**-alpha in preventing development of a colitis, a substance more effective in preventing the development of a colitis than antibodies to interferon-gamma or **tumor necrosis factor**-alpha indicating an effective substance.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . (IBD), comprising administering to a subject diagnosed with an established colitis from an IBD an amount of an antibody to **interleukin-12** effective in reducing the colitis-inducing effect of **interleukin-12**. Also provided is a method for screening a substance for its effectiveness in reducing the inflammatory response of an established. . . an animal having an established colitis; administering the substance to an animal; and assaying the animal for an effect on **interleukin-12** which results in the reduction of the inflammatory response of the colitis, an amount of reduction of the inflammatory response greater than the amount of reduction **produced** by the administration of antibodies against interferon-gamma or **tumor necrosis factor**-alpha indicating an effective substance. Additionally, the present invention provides a method for screening a substance for its effectiveness in preventing. . . comparing the effectiveness of the substance in preventing development of a colitis to the effectiveness of antibodies to interferon-gamma or **tumor necrosis factor**-alpha in preventing development of a colitis, a substance more effective in preventing the development of a colitis than antibodies to interferon-gamma or

tumor necrosis factor-alpha indicating an effective substance.

L11 ANSWER 3 OF 509 USPATFULL

ACCESSION NUMBER:	1998:150457 USPATFULL
TITLE:	Immunotherapy of cancer with allogeneic lymphocytes
INVENTOR(S):	Slavin, Shimon, Jerusalem, Israel
PATENT ASSIGNEE(S):	Hadasit Medical Research Services and Development Ltd., Israel (non-U.S. corporation) Baxter International Inc., Deerfield, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5843435		19981201	
	WO 9524910		19950921	
APPLICATION INFO.:	US 1996-714144		19960916	(8)
	WO 1995-US3303		19950316	
			19960916	PCT 371 date
			19960916	PCT 102(e) date

RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1994-214944, filed on 17 Mar 1994
DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Saunders, David
ASSISTANT EXAMINER:	VanderVegt, F. Pierre
LEGAL REPRESENTATIVE:	Buonaiuto, Mark J., Ellinger, Mark S.
NUMBER OF CLAIMS:	22
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	8 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT:	2152

AB Methods have been discovered for treating residual disease following removal of most or a substantial fraction of malignant cells from a cancer patient. An autologous stem cell transplant is performed on the patient. Following partial hematopoiesis recovery, the patient is infused with allogeneic peripheral blood lymphocytes, either alone or in combination with in vivo or in vitro T-cell activation. The infused allogeneic lymphocytes engender and anti-malignant cell response.

SUMM . . . the following: interleukin 1 (IL1), interleukin 2 (IL2), interleukin 4 (IL4), interleukin 5 (IL5), interleukin 6 (IL6), interleukin 7 (IL7), **interleukin 12** (IL12), interleukin 13 (IL13), interferon alpha (IFN.alpha.), interferon gamma (IFN.gamma.), **tumor necrosis factor** (**TNF**.alpha.), an anti-CD3 antibody or antigen-binding fragments thereof (anti-CD3), an anti-CD28 antibody or antigen-binding fragments thereof (anti-CD28), phytohemagglutinin, concanavalin-A and phorbol esters. Any of these activators can be a native factor obtained from natural sources, a factor **produced** by recombinant DNA methodology, a chemically synthesized polypeptide or other molecule, or any derivative having the functional activity of the. . .

L11 ANSWER 4 OF 509 USPATFULL

ACCESSION NUMBER:	1998:147552 USPATFULL
TITLE:	Alternative open reading frame DNA of a normal gene and a novel human cancer antigen encoded therein
INVENTOR(S):	Wang, Rong-Fu, Bethesda, MD, United States Rosenberg, Steven A., Potomac, MD, United States
PATENT ASSIGNEE(S):	The United States of America as represented by the Secretary of the Department of Health and Human Services, Washington, DC, United States (U.S.

government)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5840839		19981124
APPLICATION INFO.:	US 1996-599602		19960209 (8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: LeGuyader, John L.
ASSISTANT EXAMINER: Schwartzman, Robert
LEGAL REPRESENTATIVE: Morgan & Finnegan, L.L.P.
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 1905
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention discloses that the normal melanogenic gene, gp75 gene, encodes a gene product, a 24 amino acid peptide of ORF3, which is processed to an antigenic cancer peptide recognized by T lymphocytes. The cancer peptide of the invention derived from ORF3 is recognized by cancer antigen specific T lymphocytes as a tumor rejection antigen. The products of this gene are promising candidates for immunotherapeutic strategies for the treatment and diagnosis of patients with cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD After immunization the efficacy of the vaccine can be assessed by **production** of immune cells that recognize the cancer antigen, as assessed by specific lytic activity, specific cytokine **production**, tumor regression or combination of these. If the mammal to be immunized is already afflicted with cancer or metastasis cancer the vaccine can be administered in conjunction with other therapeutic treatments such as immunomodulators, for example, IL-2, IL-6, IL-10, **IL-12**, IL-15, interferon, **tumor necrosis factor** and the like, chemotherapeutic drugs such as cisplatinum, antiviral such as gancyclovir, amphotericin B, antibiotics and the like.

L11 ANSWER 5 OF 509 USPATFULL
ACCESSION NUMBER: 1998:143894 USPATFULL
TITLE: Secreted proteins and polynucleotides encoding them
INVENTOR(S): Jacobs, Kenneth, Newton, MA, United States
McCoy, John M., Reading, MA, United States
LaVallie, Edward R., Tewksbury, MA, United States
Racie, Lisa A., Acton, MA, United States
Merberg, David, Acton, MA, United States
Treacy, Maurice, Chestnut Hill, MA, United States
Spaulding, Vikki, Billerica, MA, United States
PATENT ASSIGNEE(S): Genetics Institute, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5837490		19981117
APPLICATION INFO.:	US 1996-739775		19961030 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-721923, filed on 27 Sep 1996, now abandoned which is a continuation-in-part of Ser. No. US 1996-664596, filed on 17 Jun 1996
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Wax, Robert A.

ASSISTANT EXAMINER: Longton, Enrique D.
LEGAL REPRESENTATIVE: Sprunger, Ph.D., Suzanne A., Brown, Scott A.
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1647
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel polynucleotides and the proteins encoded thereby are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, **TNF**, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, **IL-12**, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further. . . compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to **produce** a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may. . .

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=> s (tumor necrosis factor or TNF)/ti
L12 33602 (TUMOR NECROSIS FACTOR OR TNF)/TI

=> s (interleukin-12 or IL-12)/ti
L13 5102 (INTERLEUKIN-12 OR IL-12)/TI

=> s l12 and l13
L14 181 L12 AND L13

=> dup rem l14
PROCESSING COMPLETED FOR L14
L15 103 DUP REM L14 (78 DUPLICATES REMOVED)

=> d ibib abs

L15 ANSWER 1 OF 103 MEDLINE
ACCESSION NUMBER: 2002187762 IN-PROCESS
DOCUMENT NUMBER: 21918053 PubMed ID: 11920321
TITLE: The Role of Endogenous Interleukin (IL)-18, **IL-12**, IL-1beta, and **Tumor Necrosis Factor**-alpha in the Production of Interferon-gamma Induced by Candida albicans in Human Whole-Blood Cultures.
AUTHOR: Netea Mihai G; Stuyt Rogier J L; Kim Soo-Hyun; Van Der Meer Jos W M; Kullberg Bart Jan; Dinarello Charles A
CORPORATE SOURCE: Department of Medicine and Division of Infectious Diseases, University of Colorado Health Sciences Center, Denver, Colorado, USA and Department of Medicine, University Medical Center St. Radboud, Nijmegen, The Netherlands.. m.netea@aig.azn.nl
SOURCE: JOURNAL OF INFECTIOUS DISEASES, (2002 Apr 1) 185 (7) 963-70.
Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Abridged Index Medicus Journals; Priority Journals
ENTRY DATE: Entered STN: 20020403
Last Updated on STN: 20020403

AB Despite the importance of interferon (IFN)-gamma, tumor necrosis factor (TNF), and interleukin (IL)-18 for host defense against candidiasis, the pathways leading to their stimulation by Candida albicans are unclear. In a whole-blood model, IL-18 neutralization by IL-18 binding protein decreased C. albicans-induced IFN-gamma synthesis by 72%. Similarly, neutralization of IL-12 or IL-1beta by either neutralizing antibodies or IL-1 receptor antagonist also reduced (by 65%) IFN-gamma production. Neutralization of TNF by TNF binding proteins resulted in only a 36% reduction of IFN-gamma synthesis. In contrast, production of TNF and IL-8 was largely unaffected by these cytokine inhibitors. Thus, C. albicans stimulates IFN-gamma production in an IL-18-, IL-12-, and IL-1beta-dependent manner, whereas production of TNF and IL-8 is independent of these cytokines. Blocking the biologic activities of IL-18, IL-12, and IL-1beta in patients (e.g., for treatment of autoimmune diseases) may result in increased susceptibility to C. albicans infection.

=> d ibib abs 2-10

L15 ANSWER 2 OF 103 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:269907 CAPLUS
TITLE: Study on IL-6, IL-8, IL-10, **IL-12**, **TNF**-.alpha. levels in thoracic duct lymph and serum in bronchial asthma
AUTHOR(S): Feng, Xuebin; Liu, Feng; Wang, Jumeng; Qi, Chunsheng; Jia, Yunyi; Wang, Yunge
CORPORATE SOURCE: Department of Pediatric Resperation and Immunology (ORGANIZATION 184 Binzhou Medical College, Binzhou, 256603, Peop. Rep. China
SOURCE: Zhongguo Bingli Shengli Zazhi (2002), 18(1), 99-100
CODEN: ZBSZEB; ISSN: 1000-4718
PUBLISHER: Jinan Daxue
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The IL-6, IL-8, IL-10, IL-12, TNF-.alpha. levels in thoracic duct lymph and serum in bronchial asthma were detected. 31 middle and severe patients with thoracic duct open operation treatment were involved in anal. and the ELISA method was used. The lymph liq. on 0, 3 and 5 day and the serum on 0 and 5 day after operation were selected for detn. of IL-6, IL-8, IL-12, TNF-.alpha.. The IL-6, IL-8, IL-10, TNF-.alpha. levels in thoracic duct lymph were significantly higher than those in control serum at 0 day; the IL-6, IL-8, IL-10, TNF-.alpha. levels in thoracic duct lymph were significantly lower and IL-12 was significantly higher than those at 0 day; the serum IL-10, TNF-.alpha. levels of patients with bronchial asthma were lower and the serum IL-12 level was higher than that of control.

L15 ANSWER 3 OF 103 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001562677 MEDLINE
DOCUMENT NUMBER: 21486605 PubMed ID: 11600565
TITLE: **IL-12**, **TNF**-alpha, and hormonal changes during late pregnancy and early postpartum: implications for autoimmune disease activity during these times.
AUTHOR: Elenkov I J; Wilder R L; Bakalov V K; Link A A; Dimitrov M A; Fisher S; Crane M; Kanik K S; Chrousos G P
CORPORATE SOURCE: Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892, USA.. ije@gunet.georgetown.edu
SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, (2001 Oct) 86 (10) 4933-8.
Journal code: HRB; 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200111
ENTRY DATE: Entered STN: 20011022
Last Updated on STN: 20011105
Entered Medline: 20011101
AB Clinical observations indicate that some autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, frequently remit during pregnancy but exacerbate, or have their onset, in the postpartum period. The immune basis for these phenomena is poorly understood. Recently, excessive production of IL-12 and TNF-alpha was causally linked to rheumatoid arthritis and multiple sclerosis. We studied 18 women with normal pregnancies in their third trimester and during the early postpartum period. We report that during the third trimester pregnancy, ex vivo monocytic IL-12 production was about 3-fold and TNF-alpha production was approximately 40% lower than postpartum values. At the same time, urinary cortisol and norepinephrine excretion and serum levels of 1,25-dihydroxyvitamin were 2- to 3-fold higher than postpartum values. As shown previously, these hormones can directly suppress IL-12 and TNF-alpha production by monocytes/macrophages in vitro. We suggest that a cortisol-, norepinephrine-, and 1,25-dihydroxyvitamin-induced inhibition and subsequent rebound of IL-12 and TNF-alpha production may represent a major mechanism by which pregnancy and postpartum alter the course of or susceptibility to various autoimmune disorders.

L15 ANSWER 4 OF 103 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001208132 MEDLINE
DOCUMENT NUMBER: 21153576 PubMed ID: 11254571
TITLE: DNA from protozoan parasites Babesia bovis, Trypanosoma cruzi, and T. brucei is mitogenic for B lymphocytes and

stimulates macrophage expression of **interleukin-12, tumor necrosis factor** alpha, and nitric oxide.

AUTHOR: Shoda L K; Kegerreis K A; Suarez C E; Roditi I; Corral R S; Bertot G M; Norimine J; Brown W C

CORPORATE SOURCE: Program in Vector-Borne Diseases, Department of Veterinary Microbiology and Pathology, Washington State University, Pullman, Washington 99164, USA.

CONTRACT NUMBER: R01-AI30136 (NIAID)

SOURCE: INFECTION AND IMMUNITY, (2001 Apr) 69 (4) 2162-71.
Journal code: GO7; 0246127. ISSN: 0019-9567.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200104

ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20010417
Entered Medline: 20010412

AB The activation of innate immune responses by genomic DNA from bacteria and several nonvertebrate organisms represents a novel mechanism of pathogen recognition. We recently demonstrated the CpG-dependent mitogenic activity of DNA from the protozoan parasite Babesia bovis for bovine B lymphocytes (W. C. Brown, D. M. Estes, S. E. Chantler, K. A. Kegerreis, and C. E. Suarez, Infect. Immun. 66:5423-5432, 1998). However, activation of macrophages by DNA from protozoan parasites has not been demonstrated. The present study was therefore conducted to determine whether DNA from the protozan parasites B. bovis, Trypanosoma cruzi, and T. brucei activates macrophages to secrete inflammatory mediators associated with protective immunity. DNA from Escherichia coli and all three parasites stimulated B-lymphocyte proliferation and increased macrophage production of interleukin-12 (IL-12), tumor necrosis factor alpha (TNF-alpha), and nitric oxide (NO). Regulation of IL-12 and NO production occurred at the level of transcription. The amounts of IL-12, TNF-alpha, and NO induced by E. coli and protozoal DNA were strongly correlated (r2 > 0.9) with the frequency of CG dinucleotides in the genome, and immunostimulation by DNA occurred in the order E. coli > or = T. cruzi > T. brucei > B. bovis. Induction of inflammatory mediators by E. coli, T. brucei, and B. bovis DNA was dependent on the presence of unmethylated CpG dinucleotides. However, at high concentrations, E. coli and T. cruzi DNA-mediated macrophage activation was not inhibited following methylation. The recognition of protozoal DNA by B lymphocytes and macrophages may provide an important innate defense mechanism to control parasite replication and promote persistent infection.

L15 ANSWER 5 OF 103 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:675385 CAPLUS

DOCUMENT NUMBER: 135:343141

TITLE: Histamine inhibits chemotaxis, phagocytosis, superoxide anion production, and the production of **TNF**.alpha. and **IL-12** by macrophages via H2-receptors

AUTHOR(S): Azuma, Yasutaka; Shinohara, Mitsuko; Wang, Pao-Li; Hidaka, Atsushi; Ohura, Kiyoshi

CORPORATE SOURCE: Department of Pharmacology, Osaka Dental University, Osaka, 573-1121, Japan

SOURCE: International Immunopharmacology (2001), 1(9-10), 1867-1875
CODEN: IINMBA; ISSN: 1567-5769

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Histamine is released from stimulated basophils and mast cells, and plays an important role in the pathogenesis of allergic inflammatory processes. In vitro treatment of macrophages with histamine resulted in inhibition of chemotaxis. Moreover, histamine at 10-5 M markedly inhibited the prodn. of superoxide anions by both opsonized zymosan-A and phorbol 12-myristate 13-acetate (PMA) stimulated macrophages and histamine at a concn. range of 10-7 to 10-5 M significantly inhibited phagocytosis of Escherichia coli by macrophages. In addn., H2-selective receptor agonist dimaprit resulted in inhibition of macrophage chemotaxis and markedly inhibited the prodn. of superoxide anion by PMA-stimulated macrophages and phagocytosis of E. coli by macrophages. On the other hand, histamine and dimaprit both resulted in a concn.-dependent inhibition of lipopolysaccharide-induced prodn. of TNF.alpha. and IL-12 by macrophages. These results suggest that histamine and dimaprit may inhibit chemotaxis, phagocytosis, superoxide anion prodn., and the prodn. of TNF.alpha. and IL-12 by macrophages via H2-histamine receptors.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 6 OF 103 MEDLINE DUPLICATE 3

ACCESSION NUMBER: 2001568327 MEDLINE

DOCUMENT NUMBER: 21531601 PubMed ID: 11675375

TITLE: Signals delivered through TCR instruct **IL-12** receptor (IL-12R) expression: **IL-12** and **tumor necrosis factor**-alpha synergize for IL-12R expression at low antigen dose.

AUTHOR: Ahlers J D; Belyakov I M; Matsui S; Berzofsky J A

CORPORATE SOURCE: Molecular Immunogenetics and Vaccine Research Section, Metabolism Branch, National Cancer Institute, National Institute of Health, Bethesda, MD 20892, USA.

SOURCE: INTERNATIONAL IMMUNOLOGY, (2001 Nov) 13 (11) 1433-42. Journal code: 8916182. ISSN: 0953-8178.

PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200201

ENTRY DATE: Entered STN: 20011025
Last Updated on STN: 20020125
Entered Medline: 20020111

AB Regulation of the IL-12 receptor (IL-12R) beta2 chain has been suggested to function as a molecular switch in determining T cell phenotype. However, because most studies have been carried out under conditions in which cell proliferation was occurring, it has been difficult to distinguish between instructive and selective mechanisms in regulating this key receptor. Here, in the course of trying to understand the mechanism for synergy between IL-12 and TNF-alpha in up-regulating IFN-gamma production, we find that when the stimulus through the TCR is too weak to induce cell proliferation, which would be needed for selection, IL-12 and TNF-alpha synergize to up-regulate not only IFN-gamma, but also the IL-12Rbeta2 chain, which triggers IFN-gamma production. Neither cytokine alone was sufficient. This observation held true both in the absence of antigen-presenting cells (APC), when the stimulus was anti-CD3 on plastic, and in the presence of APC presenting ovalbumin peptide to TCR-transgenic T cells. In contrast, when the TCR signal was stronger, no cytokines were necessary to up-regulate the IL-12R. Our results support the strength of signal model in instructing Th phenotype, and suggest both an instructive role and, later, through the production of IFN-gamma, a selective role, of this synergistic combination

of cytokines in the preferential differentiation and expansion of Th1 cells.

L15 ANSWER 7 OF 103 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:550308 CAPLUS
DOCUMENT NUMBER: 136:198709
TITLE: Increased priming for **interleukin-12** and **tumor necrosis factor** .alpha. in CD64 monocytes in HIV infection: Modulation by cytokines and therapy
AUTHOR(S): Bocchino, Marialuisa; Ledru, Eric; Debord, Thierry; Gougeon, Marie-Lise
CORPORATE SOURCE: Departement SIDA et Retrovirus, Institut Pasteur, Hopital Begin, Paris, Fr.
SOURCE: AIDS (London, United Kingdom) (2001), 15(10), 1213-1223
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A key factor leading to impaired immunity in HIV infection is an alteration of the pattern of cytokine response, although its precise nature remains controversial, particularly the in vivo influence of HIV on interleukin (IL)-12 synthesis. A cross-sectional study in 73 HIV-infected persons (28 of them receiving highly active antiretroviral therapy) and 18 HIV-seroneg. healthy donors. The frequency of monocytes/macrophages (M/M) synthesizing IL-12, IL-10 and tumor necrosis factor .alpha. (TNF-.alpha.) was detd. in peripheral blood mononuclear cells. The cells were cultured in medium or were stimulated with lipopolysaccharide; proportions of CD64 M/M producing IL-12, TNF-.alpha. or IL-10 was detd. by cytofluorometric anal. The influence of exogenous interferon .gamma. (IFN-.gamma.), IL-10 or IL-15 on IL-12 synthesis was tested. Chronic HIV disease is assocd. with increased priming of M/M for IL-12 (involving both p40 and p70 mols.) and TNF-.alpha. synthesis; this was assocd. with cosynthesis of both cytokines by a fraction of M/M. Priming for IL-12 was physiol. enhanced by IFN-.gamma. and decreased by IL-10; IL-15 had no effect. The proportion of IL-10-producing CD64 M/M was not altered in patients compared with controls but there was an inverse correlation between IL-10-producing M/M and viral load. IL-12 prodn. was not correlated with viral load but was increased following antiretroviral therapy. Following LPS stimulation, IL-12 and TNF-.alpha. responses were not altered in HIV-pos. patients; however, the IL-10 response was decreased but restored by antiretroviral therapy. These observations argue for a preserved intrinsic CD64 M/M of IL-12 prodn. in HIV pathogenesis.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 8 OF 103 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:46993 CAPLUS
TITLE: Exopolysaccharides from Lactobacillus rhamnosus RW-9595M stimulate **TNF**, IL-6 and **IL-12** in human and mouse cultured immunocompetent cells, and IFN-?? in mouse splenocytes
AUTHOR(S): Chabot, Sylvie; Yu, Han-Ling; De Leseleuc, Louis; Cloutier, Denise; Van Calsteren, Marie-Rose; Lessard, Martin; Roy, Denis; Lacroix, Monique; Oth, Daniel
CORPORATE SOURCE: Microbiology and Biotechnology Research Centre, INRS-Armand-Frappier Institute, Laval, QC, H7V 1B7, Can.
SOURCE: Lait (2001), 81(6), 683-697
CODEN: LAITAG; ISSN: 0023-7302

PUBLISHER: EDP Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Exopolysaccharides (EPS) from Lactobacillus rhamnosus RW- 9595M have been prepd. from bacterial cultures, isolated, concd., fractionated and tested in vitro for their possible modulating properties on mouse splenocytes from the C57B1/6 and BALB/c strains, on the murine RAW 264.7 macrophage-like cell line and on human Peripheral Blood Mononuclear Cells (PBMC) from a total of 14 healthy donors. A first step of EPS fractionation was attempted, using membranes with different mol. wt. cut-off. Fractions were as follows: F1: >1000 kgmol-1; F2: 1000-100 kgmol-1; F3: 100-10 kgmol-1; F4: <10 kgmol-1. Total EPS, as well as F1, appeared slightly mitogenic in both mouse splenocytes and human PBMC in 2-3 d cultures, and F3 also exhibited such a property on human PBMC. Unfractionated concd. ("total") EPS, as well as F1, elicited TNF, IL-6 and IL-12 p40 both in the mouse and human cells, in 6 h and 24 h cultures, with important variability depending on the cell source. In 24 h cultures, total EPS or F1 elicited bio-active IFN- in both C57B1/6 and BALB/c splenocytes, and this IFN- secretion was sustained until at least 3 d of culture. In human PBMC, no IFN- prodn. was obsd. despite high IL-12p40 secretion. These results suggest the possibility of enhancing the immune system through EPS from lactic acid bacteria, in individuals responsive to such a stimulus.
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 9 OF 103 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:683213 CAPLUS
TITLE: Levels of NO, **TNF**-.alpha., IL-6 and **IL-12** in sera and ascites from patients with severe viral hepatitis complicated by spontaneous bacterial peritonitis and their significance
AUTHOR(S): Huang, Jiaquan; Jiang, Biwu; Chen, Yan; Zhang, Dongshen
CORPORATE SOURCE: Department of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, Peop. Rep. China
SOURCE: Tongji Yike Daxue Xuebao (2001), 30(4), 368-370
CODEN: TYDXEP; ISSN: 0258-2090
PUBLISHER: Tongji Yike Daxue
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB The possible immunopathogenic role of NO, TNF-.alpha., IL-6 and IL-12 in the patients with severe viral hepatitis (SH) complicated by spontaneous bacterial peritonitis (SBP) and their significance were studied. The levels of NO, TNF-.alpha., IL-6 and IL-12 in sera and ascites were detected by RIA(RIA) and Griess resp. in 45 patients with SH complicated by ascites, including 30 cases of SH complicated by SBH and 15 cases of SH without SBP. The levels of NO, TNF-.alpha.,IL-6 and IL-12 in sera and ascites in the patients with SH complicated by SBP were significantly higher than those without SBP($P < 0.05$), and the elevated levels of NO, TNF-.alpha., IL-6, and IL-12 were pos. correlated with serum bilirubin(SB), prothrombin time (PT) and neg. with total cholesterol(T-ch) ($P < 0.01$). When infections were controlled, the levels of NO, TNF-.alpha., IL-6 and IL-12 in sera and ascites were significantly decreased ($P < 0.05$), but only to the levels as those in the patients without SBP ($P < 0.05$). It was indicated that the abnormal elevation of NO, TNF- .alpha.,IL-6 and IL-12 in serum and ascites may dead to immunopathogenic reaction resulting in necrosis damage and endotoxemia. The combined detection of NO, TNF-.alpha., IL-6 and IL-12 might be helpful

for the early diagnosis of abdominal cavity infection and the evaluation of the disease severity and prognosis.

L15 ANSWER 10 OF 103 MEDLINE
ACCESSION NUMBER: 2002114275 MEDLINE
DOCUMENT NUMBER: 21834609 PubMed ID: 11846053
TITLE: Aspirin differentially regulates endotoxin-induced **IL-12** and **TNF**-alpha production in human dendritic cells.
AUTHOR: Ho L J; Chang D M; Shiau H Y; Chen C H; Hsieh T Y; Hsu Y L; Wong C S; Lai J H
CORPORATE SOURCE: Rheumatology/Immunology and Allergy, Department of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC.
SOURCE: SCANDINAVIAN JOURNAL OF RHEUMATOLOGY, (2001) 30 (6) 346-52. Journal code: 0321213. ISSN: 0300-9742.
PUB. COUNTRY: Norway
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020216
Last Updated on STN: 20020228
Entered Medline: 20020227

AB OBJECTIVE: In the development of autoimmune diseases, dendritic cells (DC) play critical roles. Here, we examined the effect of aspirin on lipopolysaccharide (LPS)-induced DC activation. METHODS: The monocyte-derived DC were established. The cytokine production was measured by ELISA, reverse transcriptase/polymerase chain reaction, or intracellular staining analyzed by flow cytometry. The expression of cell surface molecules was determined by flow cytometry. RESULTS: Aspirin inhibited LPS-induced DC maturation and costimulatory molecules expression. Aspirin, at therapeutic concentrations, also decreased LPS-induced IL-12 and IL-10 production. In contrast, the LPS-induced TNF-alpha production was enhanced by aspirin. The differential effects of aspirin on IL-12 and TNF-alpha production may not be due to down-regulation of cyclooxygenase activities. CONCLUSION: The various effects of aspirin on LPS-stimulated DC may influence the understanding of the diverse immunomodulatory mechanisms of this anti-inflammatory drug.

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L15 ANSWER 11 OF 103 MEDLINE DUPLICATE 4
TI **TNF**-alpha and **IL-12**: a balancing act in macrophage functioning.

L15 ANSWER 12 OF 103 MEDLINE DUPLICATE 5
TI Immunostimulatory CpG-modified plasmid DNA enhances **IL-12**, **TNF**-alpha, and NO production by bovine macrophages.

L15 ANSWER 13 OF 103 CAPLUS COPYRIGHT 2002 ACS
TI Studies on the plum components that induce **tumor necrosis factor**-.alpha. and **interleukin-12**

L15 ANSWER 14 OF 103 MEDLINE DUPLICATE 6
TI The cyclopentone prostaglandin 15-deoxy-Delta(12,14) prostaglandin J2 represses nitric oxide, **TNF**-alpha, and **IL-12** production by microglial cells.

L15 ANSWER 15 OF 103 CAPLUS COPYRIGHT 2002 ACS
TI Effects of B-16 melanoma cells and Mycoplasma pneumoniae on the induction of IL-1.beta., IL-2, IL-6, IL-10, **IL-12**, and **TNF**-.alpha. from mouse astrocytes

L15 ANSWER 16 OF 103 MEDLINE DUPLICATE 7
TI Experimental cancer cachexia: the role of host-derived cytokines interleukin (IL)-6, **IL-12**, interferon-gamma, and **tumor necrosis factor** alpha evaluated in gene knockout, tumor-bearing mice on C57 Bl background and eicosanoid-dependent cachexia.

L15 ANSWER 17 OF 103 MEDLINE DUPLICATE 8
TI Babesia bovis-stimulated macrophages express interleukin-1beta, **interleukin-12**, **tumor necrosis factor** alpha, and nitric oxide and inhibit parasite replication in vitro.

L15 ANSWER 18 OF 103 MEDLINE DUPLICATE 9
TI IL-9 protects mice from Gram-negative bacterial shock: suppression of **TNF**-alpha, **IL-12**, and IFN-gamma, and induction of IL-10.

L15 ANSWER 19 OF 103 MEDLINE DUPLICATE 10
TI Adenosine inhibits **IL-12** and **TNF**-[alpha] production via adenosine A2a receptor-dependent and independent mechanisms.

L15 ANSWER 20 OF 103 MEDLINE DUPLICATE 11
TI Inhibition of **IL-12** production in human monocyte-derived macrophages by **TNF**.

L15 ANSWER 21 OF 103 MEDLINE DUPLICATE 12
TI Antitumor effects of the combination therapy with **TNF**-alpha gene-modified tumor cells and **interleukin 12** in a melanoma model in mice.

L15 ANSWER 22 OF 103 MEDLINE DUPLICATE 13
TI Synergistic suppressive effect of double transfection of **tumor necrosis factor**-alpha and **interleukin 12** genes on tumorigenicity of Meth-A cells.

L15 ANSWER 23 OF 103 MEDLINE DUPLICATE 14
TI Aberrant macrophage cytokine production is a conserved feature among autoimmune-prone mouse strains: elevated interleukin (**IL**)-**12** and an imbalance in **tumor necrosis factor**-alpha and IL-10 define a unique cytokine profile in macrophages from young nonobese diabetic mice.

L15 ANSWER 24 OF 103 MEDLINE DUPLICATE 15
TI **IL-12**, IFN-gamma, and **TNF**-alpha released from mononuclear cells inhibit the spread of varicella-zoster virus at an early stage of varicella.

L15 ANSWER 25 OF 103 MEDLINE DUPLICATE 16
TI Innate resistance to experimental African trypanosomiasis: differences in cytokine (**TNF**-alpha, IL-6, IL-10 and **IL-12**) production by bone marrow-derived macrophages from resistant and susceptible mice.

L15 ANSWER 26 OF 103 CAPLUS COPYRIGHT 2002 ACS

TI ATP suppression of **interleukin-12** and **tumor necrosis factor**-.alpha. release from macrophages

L15 ANSWER 27 OF 103 MEDLINE DUPLICATE 17
TI Role of **IL-12** in macrophage activation during intracellular infection: **IL-12** and mycobacteria synergistically release **TNF**-alpha and nitric oxide from macrophages via IFN-gamma induction.

L15 ANSWER 28 OF 103 CAPLUS COPYRIGHT 2002 ACS
TI Effects on production of **TNF**-.alpha., IFN-.gamma., IL-10 and **IL-12** in lymphocytes infected by human herpesvirus 6 and 7 in vitro

L15 ANSWER 29 OF 103 MEDLINE DUPLICATE 18
TI Neuroendocrine regulation of **IL-12** and **TNF** -alpha/IL-10 balance. Clinical implications.

L15 ANSWER 30 OF 103 CAPLUS COPYRIGHT 2002 ACS
TI Nicotinamide inhibits enhanced in vitro production of **interleukin -12** and **tumor necrosis factor** -.alpha. in peripheral whole blood of people at high risk of developing Type 1 diabetes and people with newly diagnosed Type 1 diabetes

L15 ANSWER 31 OF 103 MEDLINE DUPLICATE 19
TI Human polymorphonuclear leukocytes produce **IL-12**, **TNF**-alpha, and the chemokines macrophage-inflammatory protein-1 alpha and -1 beta in response to Toxoplasma gondii antigens.

L15 ANSWER 32 OF 103 MEDLINE DUPLICATE 20
TI IL-4 inhibits the production of **TNF**-alpha and **IL-12** by STAT6-dependent and -independent mechanisms.

L15 ANSWER 33 OF 103 MEDLINE DUPLICATE 21
TI Lymphocyte activation gene-3, a MHC class II ligand expressed on activated T cells, stimulates **TNF**-alpha and **IL-12** production by monocytes and dendritic cells.

L15 ANSWER 34 OF 103 MEDLINE DUPLICATE 22
TI Anti-**IL-12** and anti-**TNF** antibodies synergistically suppress the progression of murine collagen-induced arthritis.

L15 ANSWER 35 OF 103 MEDLINE DUPLICATE 23
TI Differential regulation of rheumatoid synovial cell **interleukin-12** production by **tumor necrosis factor** alpha and CD40 signals.

L15 ANSWER 36 OF 103 MEDLINE DUPLICATE 24
TI Rapid local expression of **interleukin-12**, **tumor necrosis factor** alpha, and gamma interferon after cutaneous Francisella tularensis infection in tularemia-immune mice.

L15 ANSWER 37 OF 103 MEDLINE DUPLICATE 25
TI Enhanced sensitivity of **tumor necrosis factor** /lymphotoxin-alpha-deficient mice to Cryptococcus neoformans infection despite increased levels of nitrite/nitrate, interferon-gamma, and **interleukin-12**.

L15 ANSWER 38 OF 103 MEDLINE DUPLICATE 26

TI Differential inhibitory mechanism of cyclic AMP on **TNF**-alpha and **IL-12** synthesis by macrophages exposed to microbial stimuli.

L15 ANSWER 39 OF 103 MEDLINE DUPLICATE 27
TI Alleviation of lipopolysaccharide-induced acute liver injury in Propionibacterium acnes-primed IFN-gamma-deficient mice by a concomitant reduction of **TNF**-alpha, **IL-12**, and IL-18 production.

L15 ANSWER 40 OF 103 MEDLINE DUPLICATE 28
TI IL-2 and IL-4 counteract budesonide inhibition of GM-CSF and IL-10, but not of IL-8, **IL-12** or **TNF**-alpha production by human mononuclear blood cells.

L15 ANSWER 41 OF 103 MEDLINE DUPLICATE 29
TI Inhibition of Th1 polarization by soluble **TNF** receptor is dependent on antigen-presenting cell-derived **IL-12**.

L15 ANSWER 42 OF 103 MEDLINE DUPLICATE 30
TI Beta-estradiol-induced decrease in **IL-12** and **TNF**-alpha expression suppresses macrophage functions in the course of Listeria monocytogenes infection in mice.

L15 ANSWER 43 OF 103 MEDLINE DUPLICATE 31
TI Neutrophils from Mycobacterium avium-infected mice produce **TNF**-alpha, **IL-12**, and IL-1 beta and have a putative role in early host response.

L15 ANSWER 44 OF 103 MEDLINE
TI Ex vivo interleukin (IL)-1 beta, IL-6, **IL-12** and **tumor necrosis factor**-alpha responsiveness with monocytes from patients with head and neck carcinoma.

L15 ANSWER 45 OF 103 CAPLUS COPYRIGHT 2002 ACS
TI Production of **TNF**-.alpha. and **interleukin-12** in differentiated and activated THP-1 cells induced by Salmonella typhi

L15 ANSWER 46 OF 103 MEDLINE DUPLICATE 32
TI Interleukin 10 inhibits **TNF**-alpha production in human monocytes independently of **interleukin 12** and interleukin 1 beta.

L15 ANSWER 47 OF 103 CAPLUS COPYRIGHT 2002 ACS
TI Reduced in vitro production of interferon-gamma, interleukin-4 and **interleukin-12** and increased production of interleukin-6, interleukin-10 and **tumor necrosis factor**-alpha in systemic lupus erythematosus. weak correlations of cytokine production with disease activity

L15 ANSWER 48 OF 103 MEDLINE DUPLICATE 33
TI Biphasic regulation of the development of murine type II collagen-induced arthritis by **interleukin-12**: possible involvement of endogenous interleukin-10 and **tumor necrosis factor** alpha.

L15 ANSWER 49 OF 103 MEDLINE DUPLICATE 34
TI Amelioration of collagen-induced arthritis and suppression of interferon-gamma, **interleukin-12**, and **tumor necrosis factor** alpha production by interferon-beta gene therapy.

L15 ANSWER 50 OF 103 MEDLINE DUPLICATE 35
TI Cytokines (IFNs, **TNF**-alpha, IL-2 and **IL-12**) and animal models of cancer.

L15 ANSWER 51 OF 103 MEDLINE DUPLICATE 36
TI Hormonal regulation of **tumor necrosis factor** -alpha, **interleukin-12** and interleukin-10 production by activated macrophages. A disease-modifying mechanism in rheumatoid arthritis and systemic lupus erythematosus?.

L15 ANSWER 52 OF 103 MEDLINE DUPLICATE 37
TI Role of **TNF**-alpha in the induction of fungicidal activity of mouse peritoneal exudate cells against Cryptococcus neoformans by **IL-12** and IL-18.

L15 ANSWER 53 OF 103 CAPLUS COPYRIGHT 2002 ACS
TI Suppression of **TNF**.alpha. and **IL-12** in therapy

L15 ANSWER 54 OF 103 MEDLINE DUPLICATE 38
TI Inhibition of interferon gamma induced **interleukin 12** production: a potential mechanism for the anti-inflammatory activities of **tumor necrosis factor**.

L15 ANSWER 55 OF 103 MEDLINE DUPLICATE 39
TI IFN-gamma, **IL-12**, and **TNF**-alpha are required to maintain reduced liver pathology in mice vaccinated with Schistosoma mansoni eggs and **IL-12**.

L15 ANSWER 56 OF 103 MEDLINE DUPLICATE 40
TI The induction of nitric oxide by **interleukin-12** and **tumor necrosis factor**-alpha in human natural killer cells: relationship with the regulation of lytic activity.

L15 ANSWER 57 OF 103 MEDLINE DUPLICATE 41
TI IL-1 alpha and **TNF**-alpha are required for **IL-12**-induced development of Th1 cells producing high levels of IFN-gamma in BALB/c but not C57BL/6 mice.

L15 ANSWER 58 OF 103 MEDLINE DUPLICATE 42
TI Control of **IL-12** and IFN-gamma production in response to live or dead bacteria by **TNF** and other factors.

L15 ANSWER 59 OF 103 MEDLINE DUPLICATE 43
TI Epidermal cytokines IL-1beta, **TNF**-alpha, and **IL-12** in patients with atopic dermatitis: response to application of house dust mite antigens.

L15 ANSWER 60 OF 103 MEDLINE DUPLICATE 44
TI Regulation of **interleukin-12** by interleukin-10, transforming growth factor-beta, **tumor necrosis factor**-alpha, and interferon-gamma in human monocytes infected with Mycobacterium tuberculosis H37Ra.

L15 ANSWER 61 OF 103 MEDLINE DUPLICATE 45
TI Abnormal regulation of interferon-gamma, **interleukin-12** , and **tumor necrosis factor**-alpha in human interferon-gamma receptor 1 deficiency.

L15 ANSWER 62 OF 103 MEDLINE DUPLICATE 46

TI Small bowel enteropathy: role of intraepithelial lymphocytes and of cytokines (**IL-12**, IFN-gamma, **TNF**) in the induction of epithelial cell death and renewal.

L15 ANSWER 63 OF 103 MEDLINE DUPLICATE 47
TI The vasoactive intestinal peptide analogue RO25-1553 inhibits the production of **TNF** and **IL-12** by LPS-activated monocytes.

L15 ANSWER 64 OF 103 MEDLINE
TI Pyrrolidine dithiocarbamate augments IL-10, inhibits **TNF**-alpha, MIP-1alpha, **IL-12**, and nitric oxide production and protects from the lethal effect of endotoxin.

L15 ANSWER 65 OF 103 MEDLINE DUPLICATE 48
TI Treatment with homodimeric **interleukin-12** (**IL-12**) p40 protects mice from **IL-12**-dependent shock but not from **tumor necrosis factor** alpha-dependent shock.

L15 ANSWER 66 OF 103 MEDLINE DUPLICATE 49
TI Augmented antitumor effects of combination therapy with **interleukin-12**, cisplatin, and **tumor necrosis factor**-alpha in a murine melanoma model.

L15 ANSWER 67 OF 103 MEDLINE
TI Cytokine-in-adjuvant steering of the immune response phenotype to HIV-1 vaccine constructs: granulocyte-macrophage colony-stimulating factor and **TNF**-alpha synergize with **IL-12** to enhance induction of cytotoxic T lymphocytes.

L15 ANSWER 68 OF 103 MEDLINE DUPLICATE 50
TI IL-13 protects mice from lipopolysaccharide-induced lethal endotoxemia: correlation with down-modulation of **TNF**-alpha, IFN-gamma, and **IL-12** production.

L15 ANSWER 69 OF 103 MEDLINE DUPLICATE 51
TI A Leishmania protein that modulates interleukin (**IL**)-**12**, IL-10 and **tumor necrosis factor**-alpha production and expression of B7-1 in human monocyte-derived antigen-presenting cells.

L15 ANSWER 70 OF 103 MEDLINE DUPLICATE 52
TI Prostaglandin E2 and **tumor necrosis factor** alpha cooperate to activate human dendritic cells: synergistic activation of **interleukin 12** production.

L15 ANSWER 71 OF 103 CAPLUS COPYRIGHT 2002 ACS
TI Effects of Ganoderma lucidum on the IL-1, **TNF** and **IL-12** gene expression of macrophages

L15 ANSWER 72 OF 103 MEDLINE DUPLICATE 53
TI **Interleukin-12** and **tumor necrosis factor**-alpha levels in cerebrospinal fluid of multiple sclerosis patients.

L15 ANSWER 73 OF 103 MEDLINE DUPLICATE 54
TI Antitumor effects of the combination immunotherapy with **interleukin-12** and **tumor necrosis factor** alpha in mice.

L15 ANSWER 74 OF 103 MEDLINE DUPLICATE 55
TI Cytokine dichotomy in peripheral nervous system influences the outcome of experimental allergic neuritis: dynamics of mRNA expression for IL-1 beta, IL-6, IL-10, **IL-12**, **TNF**-alpha, **TNF**
-beta, and cytolysin.

L15 ANSWER 75 OF 103 CAPLUS COPYRIGHT 2002 ACS
TI The roles of **tumor necrosis factor**-.alpha., interleukin-1 and **interleukin-12** in murine cytomegalovirus infection

L15 ANSWER 76 OF 103 MEDLINE DUPLICATE 56
TI Characterization of early **IL-12**, IFN-alphabeta, and **TNF** effects on antiviral state and NK cell responses during murine cytomegalovirus infection.

L15 ANSWER 77 OF 103 CAPLUS COPYRIGHT 2002 ACS
TI Murine **IL-12** is involved in Calmette-Guerin bacillus-induced sensitization and is by itself sufficient to sensitize mice to the lethal effects of human **TNF**

L15 ANSWER 78 OF 103 MEDLINE DUPLICATE 57
TI **Interleukin-12** activates human gamma delta T cells: synergistic effect of **tumor necrosis factor**
-alpha.

L15 ANSWER 79 OF 103 MEDLINE DUPLICATE 58
TI **Tumor necrosis factor** alpha and **interleukin-12** contribute to resistance to the intracellular bacterium Brucella abortus by different mechanisms.

L15 ANSWER 80 OF 103 MEDLINE DUPLICATE 59
TI **Interleukin-12**-mediated resistance to Trypanosoma cruzi is dependent on **tumor necrosis factor** alpha and gamma interferon.

L15 ANSWER 81 OF 103 MEDLINE DUPLICATE 60
TI Soluble **tumor necrosis factor** receptor inhibits **interleukin 12** production by stimulated human adult microglial cells in vitro.

L15 ANSWER 82 OF 103 MEDLINE DUPLICATE 61
TI **Interleukin-12** and **tumor necrosis factor** alpha mediate innate production of gamma interferon by group B Streptococcus-treated splenocytes of severe combined immunodeficiency mice.

L15 ANSWER 83 OF 103 MEDLINE DUPLICATE 62
TI In the absence of endogenous IL-10, mice acutely infected with Toxoplasma gondii succumb to a lethal immune response dependent on CD4+ T cells and accompanied by overproduction of **IL-12**, IFN-gamma and **TNF**-alpha.

L15 ANSWER 84 OF 103 CAPLUS COPYRIGHT 2002 ACS
TI Retrovirus-elicited **interleukin-12** and **tumor necrosis factor**-.alpha. as inducers of interferon-.gamma.-mediated pathology in mouse AIDS

L15 ANSWER 85 OF 103 MEDLINE DUPLICATE 63
TI Interleukin-10, **interleukin-12**, and **tumor necrosis factor**-alpha differentially influence the

proliferation of human CD8+ and CD4+ T-cell clones.

L15 ANSWER 86 OF 103 MEDLINE DUPLICATE 64
TI Trypanosoma cruzi: IL-10, **TNF**, IFN-gamma, and **IL-12** regulate innate and acquired immunity to infection.

L15 ANSWER 87 OF 103 MEDLINE DUPLICATE 65
TI **Tumor necrosis factor**-alpha, lymphotoxin, interleukin (IL)-6, IL-10, **IL-12** and perforin mRNA expression in mononuclear cells in response to acetylcholine receptor is augmented in myasthenia gravis.

L15 ANSWER 88 OF 103 MEDLINE DUPLICATE 66
TI Augmentation of **TNF**-alpha production, NK cell activity and **IL-12** p35 mRNA expression by methionine enkephalin.

L15 ANSWER 89 OF 103 MEDLINE
TI Inhibitory effects of **interleukin 12** on retroviral gene transduction into CD34 cord blood myeloid progenitors mediated by induction of **tumor necrosis factor**-alpha.

L15 ANSWER 90 OF 103 MEDLINE DUPLICATE 67
TI Bacterial DNA induces murine interferon-gamma production by stimulation of **interleukin-12** and **tumor necrosis factor**-alpha.

L15 ANSWER 91 OF 103 MEDLINE DUPLICATE 68
TI IL-10 production is enhanced in human T cells by **IL-12** and IL-6 and in monocytes by **tumor necrosis factor**-alpha.

L15 ANSWER 92 OF 103 MEDLINE DUPLICATE 69
TI **IL-12**-induced protection against blood-stage Plasmodium chabaudi AS requires IFN-gamma and **TNF**-alpha and occurs via a nitric oxide-dependent mechanism.

L15 ANSWER 93 OF 103 MEDLINE DUPLICATE 70
TI Early **interleukin 12** production by macrophages in response to mycobacterial infection depends on interferon gamma and **tumor necrosis factor** alpha.

L15 ANSWER 94 OF 103 MEDLINE DUPLICATE 71
TI Mechanism of **interleukin 12**-mediated toxicities during experimental viral infections: role of **tumor necrosis factor** and glucocorticoids.

L15 ANSWER 95 OF 103 MEDLINE DUPLICATE 72
TI Stimulatory and inhibitory effects of interleukin (IL)-4 and IL-13 on the production of cytokines by human peripheral blood mononuclear cells: priming for **IL-12** and **tumor necrosis factor** alpha production.

L15 ANSWER 96 OF 103 MEDLINE DUPLICATE 73
TI Analysis of the interrelationship between **IL-12**, **TNF**-alpha, and IFN-gamma production during murine listeriosis.

L15 ANSWER 97 OF 103 MEDLINE DUPLICATE 74
TI Cytokine production in the central nervous system of Lewis rats with experimental autoimmune encephalomyelitis: dynamics of mRNA expression for interleukin-10, **interleukin-12**, cytolysin, **tumor necrosis factor** alpha and **tumor**

necrosis factor beta.

L15 ANSWER 98 OF 103 MEDLINE DUPLICATE 75
TI Production of gamma interferon by natural killer cells from Toxoplasma gondii-infected SCID mice: regulation by interleukin-10, **interleukin-12**, and **tumor necrosis factor** alpha.

L15 ANSWER 99 OF 103 MEDLINE DUPLICATE 76
TI Differential regulation of **interleukin-12 (IL -12)**, **tumor necrosis factor** alpha, and IL-1 beta production in human myeloid leukemia cell lines and peripheral blood mononuclear cells.

L15 ANSWER 100 OF 103 MEDLINE DUPLICATE 77
TI **Interleukin 12**, interferon gamma, and **tumor necrosis factor** alpha are the key cytokines of the generalized Shwartzman reaction.

L15 ANSWER 101 OF 103 MEDLINE
TI Activation of the human immature natural killer cell subset by **IL -12** and its regulation by endogenous **TNF**-alpha and IFN-gamma secretion.

L15 ANSWER 102 OF 103 CAPLUS COPYRIGHT 2002 ACS
TI Activation of the human immature natural killer cell subset by **IL -12** and its regulation by endogenous **TNF**-.alpha. and IFN-.gamma. secretion

L15 ANSWER 103 OF 103 MEDLINE DUPLICATE 78
TI **Interleukin 12** and **tumor necrosis factor** alpha are costimulators of interferon gamma production by natural killer cells in severe combined immunodeficiency mice with listeriosis, and interleukin 10 is a physiologic antagonist.

=> d ibib abs 93, 94, 96, 89, 75, 20, 11

L15 ANSWER 93 OF 103 MEDLINE DUPLICATE 70
ACCESSION NUMBER: 95239104 MEDLINE
DOCUMENT NUMBER: 95239104 PubMed ID: 7722441
TITLE: Early **interleukin 12** production by macrophages in response to mycobacterial infection depends on interferon gamma and **tumor necrosis factor** alpha.
AUTHOR: Flesch I E; Hess J H; Huang S; Aguet M; Rothe J; Bluethmann H; Kaufmann S H
CORPORATE SOURCE: Department of Immunology, University of Ulm, Germany.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1995 May 1) 181 (5) 1615-21.
Journal code: I2V; 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950605
Last Updated on STN: 19950605
Entered Medline: 19950525
AB Interleukin 12 (IL-12) produced by macrophages immediately after infection is considered essential for activation of a protective immune response

against intracellular pathogens. In the murine Mycobacterium bovis Bacillus Calmette-Guerin (BCG) model we assessed whether early IL-12 production by macrophages depends on other cytokines. In vitro, murine bone marrow-derived macrophages produced IL-12 after infection with viable M. bovis BCG or stimulation with LPS, however, priming with recombinant interferon gamma (rIFN-gamma) was necessary. In addition, IL-12 production by these macrophages was blocked by specific anti-tumor necrosis factor alpha (TNF-alpha) antiserum. Macrophages from gene deletion mutant mice lacking either the IFN-gamma receptor or the TNF receptor 1 (p55) failed to produce IL-12 in vitro after stimulation with rIFN-gamma and mycobacterial infection. In vivo, IL-12 production was induced in spleens of immunocompetent mice early during M. bovis BCG infection but not in those of mutant mice lacking the receptors for IFN-gamma or TNF. Our results show that IL-12 production by macrophages in response to mycobacterial infection depends on IFN-gamma and TNF. Hence, IL-12 is not the first cytokine produced in mycobacterial infections.

L15 ANSWER 94 OF 103 MEDLINE DUPLICATE 71
ACCESSION NUMBER: 95173605 MEDLINE
DOCUMENT NUMBER: 95173605 PubMed ID: 7869050
TITLE: Mechanism of **interleukin 12**-mediated toxicities during experimental viral infections: role of **tumor necrosis factor** and glucocorticoids.
AUTHOR: Orange J S; Salazar-Mather T P; Opal S M; Spencer R L; Miller A H; McEwen B S; Biron C A
CORPORATE SOURCE: Division of Biology and Medicine, Brown University, Providence, Rhode Island 02912.
CONTRACT NUMBER: RO1-CA-41268 (NCI)
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1995 Mar 1) 181 (3) 901-14.
Journal code: I2V; 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950407
Last Updated on STN: 19950407
Entered Medline: 19950324

AB Interleukin 12 (IL-12) doses in excess of 100 ng/d have been shown to induce profound immunotoxicities in mice infected with lymphocytic choriomeningitis virus (LCMV). These immunotoxicities are characterized by almost complete inhibition of virus-induced CD8+ T cell expansion and CTL activation, and up to 2 log increases in viral replication. They are accompanied by induction of serum tumor necrosis factor (TNF). The studies presented here were undertaken to characterize mechanisms for the IL-12-induced toxicities and to examine expression and function of TNF in this context. Several physiological changes were induced in IL-12-treated uninfected and dramatically elevated in IL-12-treated virus-infected mice. IL-12 induced (a) decreases in body weights, > 10% in uninfected and > 20% in LCMV-infected mice; (b) elevation of circulating glucocorticoid levels to > 10 micrograms/dl in uninfected and > 20 micrograms/dl in infected mice; and (c) decreases in thymic mass, > 30% in uninfected and up to 95% in infected mice. These changes are known to be associated with circulating TNF. Northern blot and in situ hybridization analyses demonstrated that IL-12 induced TNF-alpha expression and that LCMV infection synergized with IL-12 for induction of this factor. Antibodies neutralizing TNF reversed all of the IL-12-induced toxicities in LCMV-infected mice including the immunotoxicities against CD8+ T cells and anti-viral defenses. The TNF-mediated immunotoxicities appeared to result

from an induced cellular sensitivity to the factor, as splenic leukocytes and CD8+ T cell subsets isolated from LCMV-infected mice were more sensitive to TNF-mediated cytotoxicity in culture than were equivalent populations prepared from uninfected mice. Experiments with the glucocorticoid type II receptor antagonist, RU486, demonstrated that endogenous glucocorticoids were secondary intermediaries in IL-12-induced thymic atrophy. Studies in IL-2-deficient mice showed that the synergism was dependent upon endogenous IL-2. The results delineate a unique mechanism of TNF-mediated toxicity. In addition, they have significant implications concerning potential detrimental consequences of in vivo TNF induction and of IL-12 administration for protective anti-viral responses.

L15 ANSWER 96 OF 103 MEDLINE DUPLICATE 73
ACCESSION NUMBER: 95330827 MEDLINE
DOCUMENT NUMBER: 95330827 PubMed ID: 7606797
TITLE: Analysis of the interrelationship between **IL-12**, **TNF**-alpha, and IFN-gamma production during murine listeriosis.
AUTHOR: Liu W; Kurlander R J
CORPORATE SOURCE: Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710, USA.
CONTRACT NUMBER: RO1 AI18073 (NIAID)
SOURCE: CELLULAR IMMUNOLOGY, (1995 Jul) 163 (2) 260-7.
Journal code: CQ9; 1246405. ISSN: 0008-8749.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950828
Last Updated on STN: 19950828
Entered Medline: 19950817

AB IL-12, a recently described cytokine, is an important mediator in the early production of IFN-gamma during infection. To evaluate the timing of IL-12 production, and its relationship to TNF-alpha, and IFN-gamma production during primary murine listeriosis, we measured cytokine mRNA and protein levels in C57B1/6 mice infected intravenously with Listeria monocytogenes (LM). IL-12 is a disulfide-linked heterodimer containing two chains (designated P35 and P40); however, bioactive cytokine production has been more closely linked with P40 expression. Consequently, we monitored mRNA and protein levels of P40 in the spleen as a marker for IL-12 production in vivo. Splenic P40 mRNA levels (assayed using RNase protection methods) were low in uninfected animals, but increased markedly beginning 15 to 18 hr after LM infection. In sublethally infected animals, P40 mRNA levels remained elevated for 5 days, returning to baseline with the resolution of infection. P40 protein (assayed using an antibody capture ELISA) could be detected in the spleens of LM-infected animals beginning around 18 hr postinfection confirming linkage between P40 mRNA accumulation and the generation of a protein product. In comparing P40 and IFN-gamma mRNA levels in vivo, we found in each case that substantial increases in mRNA accumulation did not appear until 15-18 hr postinfection. In comparable studies using BALB/c animals, cytokine production began slightly earlier (between 12 and 15 hr) but once again P40 and IFN-gamma mRNA levels increased in a coordinated manner. P40 mRNA (like IFN-gamma and TNF-alpha mRNA) only accumulated in animals infused with live, virulent bacteria. Although we could detect no obvious lag between the time of onset of IL-12 and IFN-gamma accumulation in vivo, infusions of anti-IL-12 antibodies markedly reduced IFN-gamma expression implying that IL-12 production precedes and directs IFN-gamma production. TNF-alpha production, on the other hand, was not diminished by anti-IL-12 treatment. Our studies demonstrate that IL-12 generation is an essential

step in normal IFN-gamma production during listeriosis, and suggest that IL-12, once produced, may begin enhancing IFN-gamma production in vivo in less than 3 hr.

L15 ANSWER 89 OF 103 MEDLINE
ACCESSION NUMBER: 96304841 MEDLINE
DOCUMENT NUMBER: 96304841 PubMed ID: 8723796
TITLE: Inhibitory effects of **interleukin 12** on retroviral gene transduction into CD34 cord blood myeloid progenitors mediated by induction of **tumor necrosis factor**-alpha.
AUTHOR: Xiao M; Li Z H; McMahel J; Broxmeyer H E; Lu L
CORPORATE SOURCE: Department of Medicine (Hematology/Oncology), Indiana University School of Medicine, Indianapolis, USA.
CONTRACT NUMBER: R01 HL46549 (NHLBI)
R01 HL54037 (NHLBI)
R37 CA36464 (NCI)
+
SOURCE: JOURNAL OF HEMATOTHERAPY, (1996 Apr) 5 (2) 171-7.
Journal code: B3T; 9306048. ISSN: 1061-6128.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961022
Last Updated on STN: 19980206
Entered Medline: 19961009

AB Interleukin 12 (IL-12), a heterodimeric cytokine with potent biologic activity, was evaluated for effects on retroviral-mediated gene transduction into human myeloid progenitor cells in vitro. Cord blood CD34 cells were prestimulated with Steel factor (SLF), IL-3, GM-CSF, and erythropoietin (Epo) in the presence and absence of 5-80 ng/ml IL-12 for 40 hr in suspension culture prior to gene transduction using viral supernatant collected from a packaging cell line containing the pLNL6 vector encoding Neo sequences. After gene transduction, cells were assayed for colony formation stimulated by Epo, GM-CSF, IL-3, and SLF, and gene transduction efficiency was determined by the percentage of G418 resistant (R) colonies and confirmed by PCR analysis. IL-12 dose-dependently inhibited retroviral-mediated gene transduction into human cord blood CD34 granulocyte-macrophage (CFU-GM) and erythroid (BFU-E) progenitors. These suppressive effects could be neutralized by incubation of IL-12 with polyclonal antihuman IL-12. IL-12 had no inhibitory effects directly on colony formation. To understand the possible mechanisms for this suppression, ELISA assays were used to detect the release of interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha, which could potentially have been induced by IL-12 from CD34 cells. TNF-alpha protein release was significantly increased in CD34 cells incubated with IL-12. No detectable levels of IFN-gamma were noted. Anti-TNF-alpha, but not anti-IFN-gamma, blocked the inhibitory effects of IL-12 on gene transduction. Moreover, TNF-alpha, but not IFN-gamma, suppressed gene transfer to the same degree as IL-12. No change of amphotropic receptor mRNA expression was noted by Northern blot analysis in cells treated with or without IL-12. The results suggest that the suppressive effects of IL-12 on retroviral gene transduction are, at least in part, mediated by IL-12 induction of the release of TNF-alpha.

L15 ANSWER 75 OF 103 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:318504 CAPLUS
DOCUMENT NUMBER: 127:32682
TITLE: The roles of **tumor necrosis**

factor-.alpha., interleukin-1 and **interleukin-12** in murine cytomegalovirus infection

AUTHOR(S): Yerkovich, S. T.; Olver, S. D.; Lenzo, J. C.; Peacock, C. D.; Price, P.

CORPORATE SOURCE: Department Microbiology, University Western Australia, Nedlands, WA 6009, Australia

SOURCE: Immunology (1997), 91(1), 45-52
CODEN: IMMUAM; ISSN: 0019-2805

PUBLISHER: Blackwell

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The roles of the inflammatory cytokines tumor necrosis factor-.alpha. (TNF-.alpha.), interleukin-1 (IL-1) and IL-12, in murine cytomegalovirus (MCMV) disease were investigated in susceptible BALB/c and resistant C57BL/6 mice. MCMV infection induced IL-1 and TNF-.alpha. prodn. by peritoneal cells from BALB/c mice, as demonstrated previously in C57BL/6 mice. Overt ill-health and viral replication in the spleens of BALB/c mice were increased by in vivo treatment with sol. TNF-.alpha. receptors to inhibit the activity of this cytokine, while antibodies to IL-12 had a similar but more restricted effect. C57BL/6 mice were not affected by either treatment, suggesting TNF-.alpha. and IL-12 are not crit. for natural killer cell-mediated restriction of viral replication in the spleen. Sol. TNF-.alpha. receptors and antibodies to IL-12 also enhanced MCMV titers and nos. of viral antigen-pos. cells in the livers of BALB/c mice and TNF-.alpha. receptors have similar effects in C57BL/6 livers. In contrast, IL-1 receptors improved the health of MCMV-infected BALB/c mice and reduced viral replication and hepatitis at some time-points. Mechanisms which may underlie these changes are discussed.

L15 ANSWER 20 OF 103 MEDLINE DUPLICATE 11

ACCESSION NUMBER: 2000126031 MEDLINE

DOCUMENT NUMBER: 20126031 PubMed ID: 10657616

TITLE: Inhibition of **IL-12** production in human monocyte-derived macrophages by **TNF**.

AUTHOR: Ma X; Sun J; Papasavvas E; Riemann H; Robertson S; Marshall J; Bailer R T; Moore A; Donnelly R P; Trinchieri G; Montaner L J

CORPORATE SOURCE: The Wistar Institute, Philadelphia, PA 19104, USA.

CONTRACT NUMBER: AI40379 (NIAID)
AI43206 (NIAID)
AI44304 (NIAID)
+

SOURCE: JOURNAL OF IMMUNOLOGY, (2000 Feb 15) 164 (4) 1722-9.
Journal code: IFB; 2985117R. ISSN: 0022-1767.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200003

ENTRY DATE: Entered STN: 20000320
Last Updated on STN: 20000320
Entered Medline: 20000309

AB IL-12 is a pivotal cytokine that links the innate and adaptive immune responses. TNF-alpha also plays a key role in orchestrating inflammation and immunity. The reciprocal influence of these two inflammatory mediators on each other may have significant impact on the cytokine balance that shapes the type and extent of immune responses. To investigate the relationship between TNF-alpha and IL-12 production, we analyzed the effects of exposure of human monocyte-derived macrophages to TNF-alpha on LPS- or Staphylococcus aureus-induced IL-12 production in the presence or

absence of IFN-gamma. TNF-alpha is a potent inhibitor of IL-12 p40 and p70 secretion from human macrophages induced by LPS or S. aureus. IL-10 is not responsible for the TNF-alpha-mediated inhibition of IL-12. TNF-alpha selectively inhibits IL-12 p40 steady-state mRNA, but not those of IL-12 p35, IL-1alpha, IL-1beta, or IL-6. Nuclear run-on analysis identified this specific inhibitory effect at the transcriptional level for IL-12 p40 without down-regulation of the IL-12 p35 gene. The major transcriptional factors identified to be involved in the regulation of IL-12 p40 gene expression by LPS and IFN-gamma, i.e., c-Rel, NF-kappaB p50 and p65, IFN regulatory factor-1, and ets-2, were not affected by TNF-alpha when examined by nuclear translocation and DNA binding. These data demonstrate a selective negative regulation on IL-12 by TNF-alpha, identifying a direct negative feedback mechanism for inflammation-induced suppression of IL-12 gene expression.

L15 ANSWER 11 OF 103 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001421991 MEDLINE
DOCUMENT NUMBER: 21150811 PubMed ID: 11251298
TITLE: **TNF**-alpha and **IL-12**: a balancing act in macrophage functioning.
AUTHOR: Ma X
CORPORATE SOURCE: Department of Microbiology and Immunology, Weill Medical College of Cornell University, 1300 York Avenue, New York, NY 10021, USA.. xim2002@med.cornell.edu
CONTRACT NUMBER: AI45899 (NIAID)
CA79772 (NCI)
SOURCE: Microbes Infect, (2001 Feb) 3 (2) 121-9. Ref: 66
Journal code: DJ1; 100883508. ISSN: 1286-4579.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010730
Last Updated on STN: 20010730
Entered Medline: 20010726
AB Tumor necrosis factor alpha (TNF-alpha) and interleukin 12 (IL-12) are two major macrophage-derived mediators of inflammatory responses in mammals. Increasing evidence suggests that TNF-alpha is a double-edged sword with both proinflammatory and anti-inflammatory propensities. This article discusses the inter-regulation of TNF-alpha and IL-12 and the impact on the function of macrophages in innate and adaptive immunity.

=> fil stng

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	40.78	90.70

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.72	-3.72

FILE 'STNGUIDE' ENTERED AT 14:52:30 ON 26 APR 2002

FILE CONTAINS CURRENT INFORMATION.

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LAST RELOADED: Apr 19, 2002 (20020419/UP).

=> fil medl capl
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                          ENTRY    SESSION
FULL ESTIMATED COST                                         0.36      91.06

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                          ENTRY    SESSION
CA SUBSCRIBER PRICE                                         0.00      -3.72

FILE 'MEDLINE' ENTERED AT 14:56:02 ON 26 APR 2002

FILE 'CAPLUS' ENTERED AT 14:56:02 ON 26 APR 2002
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     (FILE 'HOME' ENTERED AT 14:14:55 ON 26 APR 2002)

     FILE 'MEDLINE, CAPLUS, BIOSIS, USPATFULL, WPIDS' ENTERED AT 14:15:15 ON
     26 APR 2002
L1        187760 S TUMOR NECROSIS FACTOR OR TNF
L2         22391 S INTERLEUKIN-12 OR IL-12
L3          6678 S L1 AND L2
L4          4764 S L1 (S) L2
L5       9931087 S PRODUC?
L6          2579 S L4 (S) L5
L7          1128 S L6 AND PY>1999
L8          1582 S L6 AND PY>1998
L9          1451 S L6 NOT PY>1999
L10          997 S L6 NOT PY>1998
L11          509 DUP REM L10 (488 DUPLICATES REMOVED)

     FILE 'STNGUIDE' ENTERED AT 14:21:53 ON 26 APR 2002

     FILE 'MEDLINE, CAPLUS' ENTERED AT 14:39:29 ON 26 APR 2002
L12        33602 S (TUMOR NECROSIS FACTOR OR TNF)/TI
L13         5102 S (INTERLEUKIN-12 OR IL-12)/TI
L14          181 S L12 AND L13
L15          103 DUP REM L14 (78 DUPLICATES REMOVED)

     FILE 'STNGUIDE' ENTERED AT 14:52:30 ON 26 APR 2002

     FILE 'MEDLINE, CAPLUS' ENTERED AT 14:56:02 ON 26 APR 2002

=> s l1
L16      104334 L1

=> s l2
L17       13000 L2

=> s (produc? or enhanc? or increas?) (a3) l2
MISSING OPERATOR INCREAS?) (A3
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s (produc? or enhanc? or increas?) (3a) l2
L18        4423 (PRODUC? OR ENHANC? OR INCREAS?) (3A) L2
```

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=> s l16 (s) l18
L19         748 L16 (S) L18

=> dup rem l19
PROCESSING COMPLETED FOR L19
L20         513 DUP REM L19 (235 DUPLICATES REMOVED)

=> d ibib abs kwic

L20  ANSWER 1 OF 513  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:216051  CAPLUS
DOCUMENT NUMBER:          136:241664
TITLE:                    Pharmaceutical composition for preventing or treating
                          a disease associated with an excess of IL-12
                          production
INVENTOR(S):              Moulon, Corinne; Heysteck, Heleen
PATENT ASSIGNEE(S):       Warner-Lambert Company, USA
SOURCE:                   Eur. Pat. Appl., 29 pp.
                          CODEN: EPXXDW
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     EP 1188438         A1   20020320       EP 2000-402560   20000915
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
     EP 1199074         A1   20020424       EP 2001-402325   20010910
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
     NO 2001004414      A    20020318       NO 2001-4414     20010911
     WO 2002022112      A2   20020321       WO 2001-EP10590  20010913
         W:  CO
PRIORITY APPLN. INFO.:                    EP 2000-402560   A  20000915
AB   The invention is directed to the use of a PDE4 inhibitor for manufg. a
     medicament for preventing and/ or treating a disease assocd. with an
     excess in IL-12 prodn. as well as to a method for treating such disorders
     through the use of at least one PDE4 inhibitor.  It is also related to a
     pharmaceutical compn. for preventing and/or treating a disease assocd.
     with an excess in IL-12 prodn. comprising an effective amt. of at least
     one PDE4 inhibitor.  Diseases assocd. with an excess in IL-12 prodn.
     encompass autoimmune disorders like inflammation of the
     bronchi/pathologies affecting the bronchus (bronchorestriction), multiple
     organ failure, osteoarthritis, septic shock (septicemia), inflammatory
     complaints or disorders, etc.
REFERENCE COUNT:          21    THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT   Tumor necrosis factors
     RL: ADV (Adverse effect, including toxicity); BSU (Biological study,
     unclassified); BIOL (Biological study)
        (in ischemia-induced reperfusion damage; pharmaceutical compn. for
        preventing or treating a disease assocd. with excess of IL-
        12 prodn. such as inflammatory disease using
        phosphodiesterase IV inhibitors)


=> focus
PROCESSING COMPLETED FOR L20
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L21 513 FOCUS L20 1-

=> d ibib abs kwic 1-10

L21 ANSWER 1 OF 513 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:122463 CAPLUS
DOCUMENT NUMBER: 133:149002
TITLE: Reduced in vitro production of interferon-gamma, interleukin-4 and **interleukin-12** and **increased production** of interleukin-6, interleukin-10 and **tumor necrosis factor**-alpha in systemic lupus erythematosus. weak correlations of cytokine production with disease activity
AUTHOR(S): Jones, Brian M.; Liu, Tiefu; Wong, Raymond W. S.
CORPORATE SOURCE: Department of Pathology, Division of Immunology Queen Mary Hospital, University of Hong Kong, Hong Kong
SOURCE: Autoimmunity (1999), 31(2), 117-124
CODEN: AUIMEI; ISSN: 0891-6934
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Prodn. of cytokines in unstimulated and mitogen-stimulated cultures were evaluated by ELISPOT in 34 SLE patients with low to moderate disease activity and 23 healthy controls. Significantly reduced prodn. of IFN.gamma., IL4 and IL12 and significantly increased prodn. of IL6, IL10 and TNF.alpha. were found in patients with SLE. Regression anal. revealed that prodn. of all six cytokines tended to decrease with increasing disease activity, but neg. correlation with SLEDAI was significant only for PHA-stimulated IL4, unstimulated and PHA-stimulated IL10 and SAC-stimulated IL6. Neg. correlation of stimulated and unstimulated IL6 and TNF.alpha. prodn. with anti-DNA antibody levels were also significant.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
TI Reduced in vitro production of interferon-gamma, interleukin-4 and **interleukin-12** and **increased production** of interleukin-6, interleukin-10 and **tumor necrosis factor**-alpha in systemic lupus erythematosus. weak correlations of cytokine production with disease activity

L21 ANSWER 2 OF 513 MEDLINE
ACCESSION NUMBER: 2001463210 MEDLINE
DOCUMENT NUMBER: 21399312 PubMed ID: 11508577
TITLE: Interferon-gamma enhances interleukin 12 production in rheumatoid synovial cells via CD40-CD154 dependent and independent pathways.
AUTHOR: Kitagawa M; Suzuki H; Adachi Y; Nakamura H; Yoshino S; Sumida T
CORPORATE SOURCE: Department of Internal Medicine, Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan.
SOURCE: JOURNAL OF RHEUMATOLOGY, (2001 Aug) 28 (8) 1764-71.
Journal code: 7501984. ISSN: 0315-162X.
PUB. COUNTRY: Canada
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20010820
Last Updated on STN: 20020128
Entered Medline: 20020125
AB OBJECTIVE: To determine the role of interferon-gamma (IFN-gamma) in

CD40-CD154 dependent **production** of **interleukin 12 (IL-12)** by synovial cells of patients with rheumatoid arthritis (RA). METHODS: We examined the effects of IFN-gamma, **tumor necrosis factor**-alpha (**TNF**-alpha), and granulocyte-macrophage colony stimulating factor (GM-CSF) on CD40 expression on CD68+ synovial macrophage-lineage cells (SMC). The effects of IFN-gamma and soluble CD154 (sCD154) on **IL-12 production** by RA synovial cells were determined by ELISA. RESULTS: CD68+ SMC expressed substantial levels of CD40. IFN-gamma, but not **TNF**-alpha or GM-CSF, markedly upregulated CD40 expression on CD68+ SMC. IFN-gamma also dose dependently **increased IL-12 production** by synovial cells. The effects of IFN-gamma on CD40 expression (EC50 = 127.4 U/ml) were observed at a concentration 19 times lower than the effects on **IL-12 production** (EC50 = 6.8 U/ml). Treatment with IFN-gamma at a concentration low enough to augment CD40 expression but not **IL-12 production enhanced** spontaneous **IL-12 production** synergy with sCD 154. The synergistic **enhancement** of spontaneous **IL-12 production** was abrogated by CD40-Fc. In contrast, **IL-12 production** induced by high concentration of IFN-gamma was not neutralized by CD40-Fc. CONCLUSION: IFN-gamma **enhanced IL-12 production** via both CD40-CD154 dependent and independent pathways in RA synovium. IFN-gamma may play a crucial role in the development of RA synovitis through regulation of **IL-12 production**.

AB OBJECTIVE: To determine the role of interferon-gamma (IFN-gamma) in CD40-CD154 dependent **production** of **interleukin 12 (IL-12)** by synovial cells of patients with rheumatoid arthritis (RA). METHODS: We examined the effects of IFN-gamma, **tumor necrosis factor**-alpha (**TNF**-alpha), and granulocyte-macrophage colony stimulating factor (GM-CSF) on CD40 expression on CD68+ synovial macrophage-lineage cells (SMC). The effects of IFN-gamma and soluble CD154 (sCD154) on **IL-12 production** by RA synovial cells were determined by ELISA. RESULTS: CD68+ SMC expressed substantial levels of CD40. IFN-gamma, but not **TNF**-alpha or GM-CSF, markedly upregulated CD40 expression on CD68+ SMC. IFN-gamma also dose dependently **increased IL-12 production** by synovial cells. The effects of IFN-gamma on CD40 expression (EC50 = 127.4 U/ml) were observed at a concentration 19 times lower than the effects on **IL-12 production** (EC50 = 6.8 U/ml). Treatment with IFN-gamma at a concentration low enough to augment CD40 expression but not **IL-12 production enhanced** spontaneous **IL-12 production** synergy with sCD 154. The synergistic **enhancement** of spontaneous **IL-12 production** was abrogated by CD40-Fc. In contrast, **IL-12 production** induced by high concentration of IFN-gamma was not neutralized by CD40-Fc. CONCLUSION: IFN-gamma **enhanced IL-12 production** via both CD40-CD154 dependent and independent pathways in RA synovium. IFN-gamma may play a crucial role in the development of RA synovitis through regulation of **IL-12 production**.

L21 ANSWER 3 OF 513 MEDLINE
ACCESSION NUMBER: 1999441966 MEDLINE
DOCUMENT NUMBER: 99441966 PubMed ID: 10513808
TITLE: Differential regulation of rheumatoid synovial cell **interleukin-12 production** by **tumor necrosis factor** alpha and CD40 signals.

AUTHOR: Kitagawa M; Mitsui H; Nakamura H; Yoshino S; Miyakawa S; Ochiai N; Onobori M; Suzuki H; Sumida T
CORPORATE SOURCE: Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan.
SOURCE: ARTHRITIS AND RHEUMATISM, (1999 Sep) 42 (9) 1917-26.
Journal code: 90M; 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991027
AB OBJECTIVE: To investigate the roles of **tumor necrosis factor** alpha(TNFalpha) and the CD40-CD154 interaction in **interleukin-12 (IL-12) production** by rheumatoid synovial cells (SC). METHODS: Levels of IL-12 (p40 and p70) in synovial tissue and culture supernatants of SC from patients with rheumatoid arthritis (RA), osteoarthritis (OA), and ankylosing spondylitis (AS) were assayed by enzyme-linked immunosorbent assay. Effects of anti-CD154 and anti-TNFalpha antibody on spontaneous and lipopolysaccharide (LPS)-stimulated **IL-12 production** by SC were examined. Effects of immobilized anti-CD3 treatment and depletion of CD4+ T cells on **IL-12 production** were also tested. CD154 expression by synovial T cells and intracellular **IL-12 production** during culture were analyzed by flow cytometry. RESULTS: IL-12 p40 and p70 levels in RA synovial tissue and spontaneous **IL-12** p40 **production** by SC from RA patients were significantly higher than the levels in OA and AS patients. Spontaneous **IL-12 production** by SC from RA patients significantly decreased after depletion of CD4+ T cells from SC or after application of anti-CD154 antibody, but not by treatment with anti-TNFalpha antibody. Anti-CD3 antibody stimulation **increased** spontaneous **IL-12** p40 **production** and CD154 expression by synovial T cells. The increment of **IL-12** p40 **production** by anti-CD3 was abrogated by anti-CD154 antibody. **IL-12** p40 **production** was also increased by LPS stimulation. LPS-stimulated **IL-12 production** was inhibited by anti-TNFalpha antibody, but not by T cell depletion and anti-CD154 antibody treatment. The TNFalpha inhibitor rolipram inhibited LPS-stimulated **IL-12** p40 **production** by RA SC more strongly than spontaneous production. TNFalpha restored LPS-stimulated **IL-12 production** that had been inhibited by rolipram. CONCLUSION: **IL-12 production** in RA is regulated by 2 different pathways. One pathway is T cell dependent, predominantly through a CD40-CD154 interaction, while the other is T cell independent, mediated through TNFalpha. Inhibition of **IL-12 production** by interference with CD40-CD154 interaction and TNFalpha production may be a potential therapeutic strategy for treating RA.
TI Differential regulation of rheumatoid synovial cell **interleukin-12 production** by **tumor necrosis factor** alpha and CD40 signals.
AB OBJECTIVE: To investigate the roles of **tumor necrosis factor** alpha(TNFalpha) and the CD40-CD154 interaction in **interleukin-12 (IL-12) production** by rheumatoid synovial cells (SC). METHODS: Levels of IL-12 (p40 and p70) in synovial tissue and culture supernatants of SC. . . ankylosing spondylitis (AS) were assayed by enzyme-linked immunosorbent

assay. Effects of anti-CD154 and anti-TNFalpha antibody on spontaneous and lipopolysaccharide (LPS)-stimulated **IL-12** **production** by SC were examined. Effects of immobilized anti-CD3 treatment and depletion of CD4+ T cells on **IL-12** **production** were also tested. CD154 expression by synovial T cells and intracellular **IL-12** **production** during culture were analyzed by flow cytometry. RESULTS: IL-12 p40 and p70 levels in RA synovial tissue and spontaneous **IL-12** p40 **production** by SC from RA patients were significantly higher than the levels in OA and AS patients. Spontaneous **IL-12** **production** by SC from RA patients significantly decreased after depletion of CD4+ T cells from SC or after application of anti-CD154 antibody, but not by treatment with anti-TNFalpha antibody. Anti-CD3 antibody stimulation **increased** spontaneous **IL-12** p40 **production** and CD154 expression by synovial T cells. The increment of **IL-12** p40 **production** by anti-CD3 was abrogated by anti-CD154 antibody. **IL-12** p40 **production** was also increased by LPS stimulation. LPS-stimulated **IL-12** **production** was inhibited by anti-TNFalpha antibody, but not by T cell depletion and anti-CD154 antibody treatment. The TNFalpha inhibitor rolipram inhibited LPS-stimulated **IL-12** p40 **production** by RA SC more strongly than spontaneous production. TNFalpha restored LPS-stimulated **IL-12** **production** that had been inhibited by rolipram. CONCLUSION: **IL-12** **production** in RA is regulated by 2 different pathways. One pathway is T cell dependent, predominantly through a CD40-CD154 interaction, while the other is T cell independent, mediated through TNFalpha. Inhibition of **IL-12** **production** by interference with CD40-CD154 interaction and TNFalpha production may be a potential therapeutic strategy for treating RA.

L21 ANSWER 4 OF 513 MEDLINE
ACCESSION NUMBER: 2000137083 MEDLINE
DOCUMENT NUMBER: 20137083 PubMed ID: 10674618
TITLE: Injury induces deficient interleukin-12 production, but interleukin-12 therapy after injury restores resistance to infection.
AUTHOR: Goebel A; Kavanagh E; Lyons A; Saporoschetz I B; Soberg C; Lederer J A; Mannick J A; Rodrick M L
CORPORATE SOURCE: Department of Surgery, Brigham and Women's Hospital/Harvard Medical School, Boston, Massachusetts, USA.
CONTRACT NUMBER: R01GM3563314 (NIGMS)
SOURCE: ANNALS OF SURGERY, (2000 Feb) 231 (2) 253-61.
Journal code: 67S; 0372354. ISSN: 0003-4932.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000320
Last Updated on STN: 20000320
Entered Medline: 20000309

AB OBJECTIVE: To assess at serial intervals the **production** of **interleukin-12** (**IL-12**) by monocytes/macrophages from the peripheral blood of injured patients and control subjects, and using a mouse model to confirm human findings and explore the effectiveness of low-dose IL-12 therapy in restoring resistance to infection after injury. SUMMARY BACKGROUND DATA: Serious injury is associated with loss of function of the T helper 1 lymphocyte phenotype, but little is known about **IL-12**

production in injured patients. The authors previously reported that early, moderate-dose IL-12 therapy in a mouse model of burn injury restored resistance to a later infectious challenge (cecal ligation and puncture, CLP). However, the efficacy of clinically relevant low-dose IL-12 therapy carried out to or beyond the time of septic challenge remains to be tested. METHODS: Peripheral blood mononuclear cells (PBMCs) and adherent cells were obtained from 27 patients with major burns or traumatic injury and 18 healthy persons and were studied at serial intervals for **IL-12 production** stimulated by bacterial lipopolysacharide (LPS). PBMCs from 18 of the same patients were studied for IL-10 **production** as well. **IL-12 production** by adherent cells from the spleens of burn or sham burn mice was studied at serial intervals after injury to confirm the human findings. Low-dose IL-12 or vehicle was given every other day to groups of burn and sham burn mice, which were then challenged with CLP on day 10, and survival was determined. Finally, spleens were harvested from burn or sham burn animals receiving low-dose IL-12 or vehicle after CLP. After splenic cellularity was determined by hemocytometer, splenocytes were cultured and production of **tumor necrosis factor**-alpha, interferon-gamma, and IL-10 were assessed by immunoassay. RESULTS: Adherent cells from patients' PBMCs **produced** significantly less **IL-12** than normal PBMCs after injury, reaching a nadir 8 to 14 days after injury. Stimulation of whole PBMCs by LPS indicated that at 8 to 14 days after injury, **IL-12 production** by PBMCs was significantly lower and IL-10 production was significantly higher than that of PBMCs from healthy persons. Low-dose **IL-12** therapy significantly **increased** survival after CLP. Splenocytes from burn mice treated with **IL-12** had significantly **increased production** of **TNF**-alpha and IF-beta, both before and after CLP, when compared with vehicle-treated burn animals. IL-10 production by bum splenocytes remained high after **IL-12** treatment. Splenic cellularity **increased** after **IL-12** treatment in burn mice. CONCLUSION: The capacity to **produce IL-12** by adherent cells of the monocyte/macrophage lineage is significantly reduced after serious injury in humans and in a mouse burn model. In humans, there is a reciprocal relation between diminished **IL-12 production** and **increased** IL-10 production at approximately 1 week after injury. Low-dose IL-12 therapy in the mouse burn model markedly increased survival after a septic challenge, even when treatment was carried beyond the onset of sepsis. Low-dose IL-12 treatment in the mouse increased production of proinflammatory mediators important in host defense and at the same time maintained or increased production of IL-10, an important antiinflammatory cytokine.

AB OBJECTIVE: To assess at serial intervals the **production** of **interleukin-12** (**IL-12**) by monocytes/macrophages from the peripheral blood of injured patients and control subjects, and using a mouse model to confirm human. . . Serious injury is associated with loss of function of the T helper 1 lymphocyte phenotype, but little is known about **IL-12 production** in injured patients. The authors previously reported that early, moderate-dose IL-12 therapy in a mouse model of burn injury restored. . . from 27 patients with major burns or traumatic injury and 18 healthy persons and were studied at serial intervals for **IL-12 production** stimulated by bacterial lipopolysacharide (LPS). PBMCs from 18 of the same patients were studied for IL-10 **production** as well. **IL-12 production** by adherent cells from the spleens of burn or sham burn mice was studied at serial intervals after injury to. . . receiving low-dose IL-12 or vehicle after CLP. After splenic cellularity was determined by

hemocytometer, splenocytes were cultured and production of **tumor necrosis factor**-alpha, interferon-gamma, and IL-10 were assessed by immunoassay. RESULTS: Adherent cells from patients' PBMCs **produced** significantly less **IL-12** than normal PBMCs after injury, reaching a nadir 8 to 14 days after injury. Stimulation of whole PBMCs by LPS indicated that at 8 to 14 days after injury, **IL-12 production** by PBMCs was significantly lower and IL-10 production was significantly higher than that of PBMCs from healthy persons. Low-dose **IL-12** therapy significantly **increased** survival after CLP. Splenocytes from burn mice treated with **IL-12** had significantly **increased production** of **TNF**-alpha and IF-beta, both before and after CLP, when compared with vehicle-treated burn animals. IL-10 production by bum splenocytes remained high after **IL-12** treatment. Splenic cellularity **increased** after **IL-12** treatment in burn mice. CONCLUSION: The capacity to **produce IL-12** by adherent cells of the monocyte/macrophage lineage is significantly reduced after serious injury in humans and in a mouse burn model. In humans, there is a reciprocal relation between diminished **IL-12 production** and **increased** IL-10 production at approximately 1 week after injury. Low-dose IL-12 therapy in the mouse burn model markedly increased survival after. . .

L21 ANSWER 5 OF 513 MEDLINE
ACCESSION NUMBER: 97131710 MEDLINE
DOCUMENT NUMBER: 97131710 PubMed ID: 8977211
TITLE: Antigen-driven but not lipopolysaccharide-driven IL-12 production in macrophages requires triggering of CD40.
AUTHOR: DeKruyff R H; Gieni R S; Umetsu D T
CORPORATE SOURCE: Division of Immunology and Transplantation Biology, Department of Pediatrics, Stanford University, CA 94305, USA.
CONTRACT NUMBER: KO7AI01026 (NIAID)
RO1AI24571 (NIAID)
RO1AI26322 (NIAID)
SOURCE: JOURNAL OF IMMUNOLOGY, (1997 Jan 1) 158 (1) 359-66.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970130

AB We demonstrated that two distinct pathways exist for the induction of IL-12 in APC. The first pathway for **IL-12 production** occurred during responses to T cell-dependent Ags such as OVA and required triggering of CD40 molecules on the APC. **IL-12 production** in this T cell-dependent system increased in direct proportion to Ag concentration and required TCR ligation but not CD28 costimulation. The second pathway occurred when bacterial products such as LPS or heat-killed Listeria monocytogenes were used to activate macrophages to **produce IL-12** in the complete absence of T cells. In this second pathway, **IL-12 production** was completely independent of CD40 triggering. In both pathways, the presence of IFN-gamma was not required for induction of IL-12 synthesis when splenic adherent cells (SAC) from normal mice were used. However, addition of IFN-gamma to cultures of Th2 T cells and SAC **increased IL-12 production** two- to

fivefold, and addition of rTNF-alpha with IFN-gamma further **enhanced IL-12 production**. The addition of **TNF**-alpha in the absence of IFN-gamma, however, had no effect on **IL-12 production** in the T cell-dependent pathway. Similarly, addition of **TNF**-alpha in the presence or the absence of IFN-gamma to cultures of LPS or heat-killed Listeria and SAC did not **increase IL-12 production**, but addition of IFN-gamma alone greatly **enhanced IL-12 production**, consistent with the idea that bacterial stimuli induce significant quantities of endogenous **TNF**-alpha production. These results indicate that the requirements for the induction of **IL-12 production** in T cell-dependent and T cell-independent responses differs mainly with regard to CD40 triggering. Furthermore, these results suggest that **IL-12 production** can be induced by bacterial products in patients with hyper-IgM syndrome who lack CD40 ligand expression and in those treated with soluble gp39 to interrupt CD40-CD40 ligand interactions.

AB We demonstrated that two distinct pathways exist for the induction of IL-12 in APC. The first pathway for **IL-12 production** occurred during responses to T cell-dependent Ags such as OVA and required triggering of CD40 molecules on the APC. **IL-12 production** in this T cell-dependent system increased in direct proportion to Ag concentration and required TCR ligation but not CD28 costimulation.. . . The second pathway occurred when bacterial products such as LPS or heat-killed Listeria monocytogenes were used to activate macrophages to **produce IL-12** in the complete absence of T cells. In this second pathway, **IL-12 production** was completely independent of CD40 triggering. In both pathways, the presence of IFN-gamma was not required for induction of IL-12. . . adherent cells (SAC) from normal mice were used. However, addition of IFN-gamma to cultures of Th2 T cells and SAC **increased IL-12 production** two- to fivefold, and addition of rTNF-alpha with IFN-gamma further **enhanced IL-12 production**. The addition of **TNF**-alpha in the absence of IFN-gamma, however, had no effect on **IL-12 production** in the T cell-dependent pathway. Similarly, addition of **TNF**-alpha in the presence or the absence of IFN-gamma to cultures of LPS or heat-killed Listeria and SAC did not **increase IL-12 production**, but addition of IFN-gamma alone greatly **enhanced IL-12 production**, consistent with the idea that bacterial stimuli induce significant quantities of endogenous **TNF**-alpha production. These results indicate that the requirements for the induction of **IL-12 production** in T cell-dependent and T cell-independent responses differs mainly with regard to CD40 triggering. Furthermore, these results suggest that **IL-12 production** can be induced by bacterial products in patients with hyper-IgM syndrome who lack CD40 ligand expression and in those treated. . .

L21 ANSWER 6 OF 513 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:764714 CAPLUS
DOCUMENT NUMBER: 132:206738
TITLE: Production of TNF-.alpha. and interleukin-12 in differentiated and activated THP-1 cells induced by Salmonella typhi
AUTHOR(S): Li, Tiemin; Ezaki, Tarayuki
CORPORATE SOURCE: College of Environment & Life Science, Liaoning University, Shenyang, 110036, Peop. Rep. China
SOURCE: Xibao Yu Fenzi Mianyixue Zazhi (1999), 15(3), 198-200

CODEN: XFMZFM; ISSN: 1007-8738
PUBLISHER: Disi Junyi Daxue
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB Prodn. of TNF-.alpha. and IL-12 induced by Salmonella typhi was studied in the human monocytic leukemia cell lines THP-1 which were in different differentiated and activated state in order to explore the prodn. of the cytokines in host cells induced by S. typhi and the regulatory effect of cytokines on host defense against S. typhi infection. S. typhi induced **TNF**-.alpha. and **IL-12 prodn**. in PMA-induced differentiated THP-1 cells, and also **IL-12 prodn**. both in THP-1 cells and in PMA differentiated THP-1 cells. But S. typhi did not induce TNF-.alpha. formation in PMA-non-induced THP-1 cells. IFN-.gamma. enhanced not only **TNF**-.alpha. prodn. in the THP-1 cells induced by S. typhi, but also **TNF**-.alpha. and **IL-12 prodn**. in PMA-differentiated THP-1 cells induced by S. typhi. TNF-.alpha. prodn. induced by S. typhi might be related to monocytic differentiated state and TNF-.alpha. and IL-2 prodn. might be due to different mechanisms. IFN-.gamma. maybe a physiol. regulator of **TNF**-.alpha. and **IL-12 prodn**.

AB Prodn. of TNF-.alpha. and IL-12 induced by Salmonella typhi was studied in the human monocytic leukemia cell lines THP-1 which were in different differentiated and activated state in order to explore the prodn. of the cytokines in host cells induced by S. typhi and the regulatory effect of cytokines on host defense against S. typhi infection. S. typhi induced **TNF**-.alpha. and **IL-12 prodn**. in PMA-induced differentiated THP-1 cells, and also **IL-12 prodn**. both in THP-1 cells and in PMA differentiated THP-1 cells. But S. typhi did not induce TNF-.alpha. formation in PMA-non-induced THP-1 cells. IFN-.gamma. enhanced not only **TNF**-.alpha. prodn. in the THP-1 cells induced by S. typhi, but also **TNF**-.alpha. and **IL-12 prodn**. in PMA-differentiated THP-1 cells induced by S. typhi. TNF-.alpha. prodn. induced by S. typhi might be related to monocytic differentiated state and TNF-.alpha. and IL-2 prodn. might be due to different mechanisms. IFN-.gamma. maybe a physiol. regulator of **TNF**-.alpha. and **IL-12 prodn**.

IT **Interleukin 12**
Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**prodn**. of **TNF**-.alpha. and interleukin-12 in differentiated and activated THP-1 cells induced by Salmonella typhi)

IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(.gamma., effect on **TNF**-.alpha. and **interleukin 12** formation; **prodn**. of **TNF**-.alpha. and interleukin-12 in differentiated and activated THP-1 cells induced by Salmonella typhi)

L21 ANSWER 7 OF 513 MEDLINE
ACCESSION NUMBER: 95239104 MEDLINE
DOCUMENT NUMBER: 95239104 PubMed ID: 7722441
TITLE: Early **interleukin 12 production** by macrophages in response to mycobacterial infection depends on interferon gamma and **tumor necrosis factor** alpha.
AUTHOR: Flesch I E; Hess J H; Huang S; Aguet M; Rothe J; Bluethmann H; Kaufmann S H

CORPORATE SOURCE: Department of Immunology, University of Ulm, Germany.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1995 May 1) 181 (5) 1615-21.
Journal code: I2V; 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950605
Last Updated on STN: 19950605
Entered Medline: 19950525

AB **Interleukin 12 (IL-12)** **produced** by macrophages immediately after infection is considered essential for activation of a protective immune response against intracellular pathogens. In the murine Mycobacterium bovis Bacillus Calmette-Guerin (BCG) model we assessed whether early **IL-12 production** by macrophages depends on other cytokines. In vitro, murine bone marrow-derived macrophages **produced** **IL-12** after infection with viable M. bovis BCG or stimulation with LPS, however, priming with recombinant interferon gamma (rIFN-gamma) was necessary. In addition, **IL-12** **production** by these macrophages was blocked by specific anti-**tumor necrosis factor** alpha (**TNF** -alpha) antiserum. Macrophages from gene deletion mutant mice lacking either the IFN-gamma receptor or the **TNF** receptor 1 (p55) failed to **produce IL-12** in vitro after stimulation with rIFN-gamma and mycobacterial infection. In vivo, **IL-12 production** was induced in spleens of immunocompetent mice early during M. bovis BCG infection but not in those of mutant mice lacking the receptors for IFN-gamma or **TNF**. Our results show that **IL-12 production** by macrophages in response to mycobacterial infection depends on IFN-gamma and **TNF** . Hence, IL-12 is not the first cytokine produced in mycobacterial infections.

TI Early **interleukin 12 production** by macrophages in response to mycobacterial infection depends on interferon gamma and **tumor necrosis factor** alpha.

AB **Interleukin 12 (IL-12)** **produced** by macrophages immediately after infection is considered essential for activation of a protective immune response against intracellular pathogens. In the murine Mycobacterium bovis Bacillus Calmette-Guerin (BCG) model we assessed whether early **IL-12 production** by macrophages depends on other cytokines. In vitro, murine bone marrow-derived macrophages **produced** **IL-12** after infection with viable M. bovis BCG or stimulation with LPS, however, priming with recombinant interferon gamma (rIFN-gamma) was necessary. In addition, **IL-12** **production** by these macrophages was blocked by specific anti-**tumor necrosis factor** alpha (**TNF** -alpha) antiserum. Macrophages from gene deletion mutant mice lacking either the IFN-gamma receptor or the **TNF** receptor 1 (p55) failed to **produce IL-12** in vitro after stimulation with rIFN-gamma and mycobacterial infection. In vivo, **IL-12 production** was induced in spleens of immunocompetent mice early during M. bovis BCG infection but not in those of mutant mice lacking the receptors for IFN-gamma or **TNF**. Our results show that **IL-12 production** by macrophages in response to mycobacterial infection depends on IFN-gamma and **TNF** . Hence, IL-12 is not the first cytokine produced in mycobacterial infections.

L21 ANSWER 8 OF 513 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:27406 CAPLUS
DOCUMENT NUMBER: 128:100929
TITLE: Suppression of murine type II collagen-induced arthritis by interleukin 12
AUTHOR(S): Yamazaki, Jyunko; Kasama, Tsuyoshi; Miwa, Yusuke; Hanyuuda, Michio; Hatano, Yoshimi; Kobayashi, Kazuo; Negishi, Masao; Ide, Hirotsugu; Adachi, Mitsuru
CORPORATE SOURCE: First Dept. of Internal Medicine, Showa Univ. School of Medicine, Tokyo, 142, Japan
SOURCE: Ensho (1997), 17(6), 549-555
CODEN: ENSHEE; ISSN: 0389-4290
PUBLISHER: Nippon Ensho Gakkai Jimukyoku
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB In the present study, we examd. the effect of interleukin 12 (IL-12) on the evolution of murine type II collagen-induced arthritis (CIA). CIA mice injected i.p. with IL-12 (500 ng/mouse/d) demonstrated delayed onset and reduced severity of arthritis. Although IL-12 administration augmented lymphocyte proliferation and interferon-.gamma. prodn. against specific and non-specific stimulation, anti-collagen antibody prodn. was significantly suppressed in CIA, as compared with control mice. Since **IL-12** induced the **prodn**. of serum **tumor necrosis factor** (**TNF**)-.alpha. and corticosterone, the suppression of CIA by IL-12 may, in part, depend upon the augmentation of serum corticosterone, induced by endogenous **TNF**-.alpha.. These data suggest that IL-12 is an important immunomodulator of the pathogenesis of CIA, which acts by regulating not only the humoral and cellular immune responses, but also the expression of immunoregulatory mediators.
AB In the present study, we examd. the effect of interleukin 12 (IL-12) on the evolution of murine type II collagen-induced arthritis (CIA). CIA mice injected i.p. with IL-12 (500 ng/mouse/d) demonstrated delayed onset and reduced severity of arthritis. Although IL-12 administration augmented lymphocyte proliferation and interferon-.gamma. prodn. against specific and non-specific stimulation, anti-collagen antibody prodn. was significantly suppressed in CIA, as compared with control mice. Since **IL-12** induced the **prodn**. of serum **tumor necrosis factor** (**TNF**)-.alpha. and corticosterone, the suppression of CIA by IL-12 may, in part, depend upon the augmentation of serum corticosterone, induced by endogenous **TNF**-.alpha.. These data suggest that IL-12 is an important immunomodulator of the pathogenesis of CIA, which acts by regulating not only the humoral and cellular immune responses, but also the expression of immunoregulatory mediators.

L21 ANSWER 9 OF 513 MEDLINE
ACCESSION NUMBER: 1999030651 MEDLINE
DOCUMENT NUMBER: 99030651 PubMed ID: 9811882
TITLE: Inhibition of interferon gamma induced **interleukin 12 production**: a potential mechanism for the anti-inflammatory activities of **tumor necrosis factor**.
AUTHOR: Hodge-Dufour J; Marino M W; Horton M R; Jungbluth A; Burdick M D; Strieter R M; Noble P W; Hunter C A; Pure E
CORPORATE SOURCE: Immunology Graduate Group, University of Pennsylvania, Philadelphia, PA 19104, USA.
CONTRACT NUMBER: AI42334 (NIAID)
HL50057 (NHLBI)
HL60539 (NHLBI)

+
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Nov 10) 95 (23) 13806-11. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981216

AB Inflammation is associated with production of cytokines and chemokines that recruit and activate inflammatory cells. Interleukin (**IL**) **12 produced** by macrophages in response to various stimuli is a potent inducer of interferon (IFN) gamma production. IFN-gamma, in turn, markedly **enhances IL-12 production**. Although the immune response is typically self-limiting, the mechanisms involved are unclear. We demonstrate that IFN-gamma inhibits production of chemokines (macrophage inflammatory proteins MIP-1alpha and MIP-1beta). Furthermore, pre-exposure to **tumor necrosis factor** (**TNF**) inhibited IFN-gamma priming for production of high levels of IL-12 by macrophages in vitro. Inhibition of IL-12 by **TNF** can be mediated by both IL-10-dependent and IL-10-independent mechanisms. To determine whether **TNF** inhibition of IFN-gamma-induced **IL-12 production** contributed to the resolution of an inflammatory response in vivo, the response of **TNF**+/+ and **TNF**-/- mice injected with Corynebacterium parvum were compared. **TNF**-/- mice developed a delayed, but vigorous, inflammatory response leading to death, whereas **TNF**+/+ mice exhibited a prompt response that resolved. Serum IL-12 levels were elevated 3-fold in C. parvum-treated **TNF**-/- mice compared with **TNF**+/+ mice. Treatment with a neutralizing anti-IL-12 antibody led to resolution of the response to C. parvum in **TNF**-/- mice. We conclude that the role of **TNF** in limiting the extent and duration of inflammatory responses in vivo involves its capacity to regulate macrophage **IL-12 production**. IFN-gamma inhibition of chemokine production and inhibition of IFN-gamma-induced **IL-12 production** by **TNF** provide potential mechanisms by which these cytokines can exert anti-inflammatory/repair function(s).

TI Inhibition of interferon gamma induced **interleukin 12 production**: a potential mechanism for the anti-inflammatory activities of **tumor necrosis factor**.

AB Inflammation is associated with production of cytokines and chemokines that recruit and activate inflammatory cells. Interleukin (**IL**) **12 produced** by macrophages in response to various stimuli is a potent inducer of interferon (IFN) gamma production. IFN-gamma, in turn, markedly **enhances IL-12 production**. Although the immune response is typically self-limiting, the mechanisms involved are unclear. We demonstrate that IFN-gamma inhibits production of chemokines (macrophage inflammatory proteins MIP-1alpha and MIP-1beta). Furthermore, pre-exposure to **tumor necrosis factor** (**TNF**) inhibited IFN-gamma priming for production of high levels of IL-12 by macrophages in vitro. Inhibition of IL-12 by **TNF** can be mediated by both IL-10-dependent and IL-10-independent mechanisms. To determine whether **TNF** inhibition of IFN-gamma-induced **IL-12 production** contributed to the resolution of an inflammatory response in vivo, the response of **TNF**+/+ and

TNF-/- mice injected with Corynebacterium parvum were compared. **TNF**-/- mice developed a delayed, but vigorous, inflammatory response leading to death, whereas **TNF**+/+ mice exhibited a prompt response that resolved. Serum IL-12 levels were elevated 3-fold in C. parvum-treated **TNF**-/- mice compared with **TNF**+/+ mice. Treatment with a neutralizing anti-IL-12 antibody led to resolution of the response to C. parvum in **TNF**-/- mice. We conclude that the role of **TNF** in limiting the extent and duration of inflammatory responses in vivo involves its capacity to regulate macrophage **IL-12 production**. IFN-gamma inhibition of chemokine production and inhibition of IFN-gamma-induced **IL-12 production** by **TNF** provide potential mechanisms by which these cytokines can exert anti-inflammatory/repair function(s).

L21 ANSWER 10 OF 513 MEDLINE
ACCESSION NUMBER: 95138686 MEDLINE
DOCUMENT NUMBER: 95138686 PubMed ID: 7836910
TITLE: Stimulatory and inhibitory effects of interleukin (IL)-4 and IL-13 on the production of cytokines by human peripheral blood mononuclear cells: priming for IL-12 and tumor necrosis factor alpha production.
AUTHOR: D'Andrea A; Ma X; Aste-Amezaga M; Paganin C; Trinchieri G
CORPORATE SOURCE: Wistar Institute of Anatomy and Biology, Philadelphia, Pennsylvania 19104.
CONTRACT NUMBER: CA-10815 (NCI)
CA-20833 (NCI)
CA-32898 (NCI)
+
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1995 Feb 1) 181 (2) 537-46.
Journal code: I2V; 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950314
Last Updated on STN: 19970203
Entered Medline: 19950224

AB The production of cytokines in monocytes/macrophages is regulated by several different cytokines that have activating or inhibitory effects. Interleukin (IL)-10, IL-4, IL-13, and transforming growth factor (TGF)-beta are usually considered to be the most important macrophage-deactivating factors, with inhibitory effects on cytokine production. Unlike IL-10 and TGF-beta, which appear to act as downmodulators of many phagocytic cell functions, the mode of action of IL-4 and IL-13 is more complex. Addition of IL-4 and IL-13 to peripheral blood mononuclear cell (PBMC) cultures inhibited **production** of **IL-12**, **tumor necrosis factor** (**TNF**)-alpha, IL-10, and IL-1 beta induced by lipopolysaccharide (LPS) or Staphylococcus aureus added simultaneously with the cytokines. However, pretreatment of PBMC with IL-4 or IL-13 for > or = 20 h **enhanced** the **production** of **IL-12** and **TNF**-alpha in response to LPS or S. aureus several fold in these cells; this IL-4-induced priming for the two cytokines was inhibited by anti-IL-4 neutralizing antibodies. IL-4 priming also **enhanced** the accumulation of **IL-12** and **TNF**-alpha mRNA induced by LPS and S. aureus. The enhanced accumulation of transcripts for the IL-12 p35 and p40 chains by IL-4 priming was reflected in enhanced secretion of both the IL-12 free p40 chain and the p70 heterodimer. These

results suggest an unexpected complexity in the regulatory role of IL-4 and IL-13 in immune responses.

AB . . . of IL-4 and IL-13 is more complex. Addition of IL-4 and IL-13 to peripheral blood mononuclear cell (PBMC) cultures inhibited **production** of **IL-12**, **tumor necrosis factor** (**TNF**)-alpha, IL-10, and IL-1 beta induced by lipopolysaccharide (LPS) or Staphylococcus aureus added simultaneously with the cytokines. However, pretreatment of PBMC with IL-4 or IL-13 for > or = 20 h **enhanced** the **production** of **IL-12** and **TNF**-alpha in response to LPS or S. aureus several fold in these cells; this IL-4-induced priming for the two cytokines was inhibited by anti-IL-4 neutralizing antibodies. IL-4 priming also **enhanced** the accumulation of **IL-12** and **TNF**-alpha mRNA induced by LPS and S. aureus. The enhanced accumulation of transcripts for the IL-12 p35 and p40 chains by. . .

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	34.32	125.38

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.48	-6.20

FILE 'STNGUIDE' ENTERED AT 14:59:46 ON 26 APR 2002

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Apr 19, 2002 (20020419/UP).

=>

---Logging off of STN---

Connection closed by remote host
END

Unable to generate the STN prompt.
Exiting the script...